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OSTEOMALACIA

PATHOGENESIS AND TREATMENT

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[WITH SPECIAL PLATE]

Two processes are to be distinguished in the formation of osseous tissue. First the matrix, a tissue rich in proteins, is formed by the osteoblasts. Then this matrix is calcified by precipitation of calcium phosphate. In osteomalacia the bone matrix is formed but its calcification is insufficient, and this gives rise to the development of osteoid zones—that is, non-calcified matrix—around the bone trabeculae.

The same abnormalities are found in rickets, which is only distinguished from osteomalacia in that it concerns young persons in whom the epiphyses have not yet closed, so that here also the deficient calcification becomes manifest. Owing to the insufficient calcification an adjoining osteoid zone is formed. Thus wide and irregular epiphyses develop. In adults the epiphyses are closed, so that the morbid process manifests itself only in the formation of new bone, which also regularly takes place in adults. Apart from the osteoid zones around the trabeculae on the flat and long bones, a more or less general decalcification of the skeleton is found, which is attributable to the inhibited regenerative calcification. Especially in osteomalacia, with which the present paper mainly deals, this is very characteristic.

The inadequate calcification may be the result of deficiency of calcium as compared with the inorganic phosphate level, or of a too low inorganic phosphate level with respect to the calcium content, necessary for a normal precipitation of calcium phosphate in the bone matrix. The causes of disturbed calcification may be various.

Vitamin-D Deficiency

The action of vitamin D has so far not been completely elucidated. It is, however, an established fact that under the influence of vitamin D calcium absorption from the intestine is stimulated, and, probably indirectly, also the absorption of inorganic phosphate. In the event of a deficiency a considerable quantity of the calcium and phosphate taken up with the food is therefore lost; calcium excretion in the stools increases markedly, while excretion of calcium in the urine is much decreased. The latter may be regarded as an early manifestation, as the blood calcium level may still be normal at this stage. The tubular reabsorption of inorganic phosphate is also disturbed, either as a direct result of vitamin-D deficiency or, as Albright *et al.* (1946, 1953) think, as a result of a secondary hyperparathyroidism.

In many cases the disturbed reabsorption of amino-acids, as sometimes observed in rickets, is favourably influenced by vitamin D (Jonxis, 1955a). It is further probable that vitamin D stimulates the deposition of calcium phosphate in the bone matrix.

Vitamin D is formed in the skin from 7-dehydrocholesterol under the influence of sunlight (ultraviolet rays). Lack of sunshine will therefore promote the development of osteomalacia. When the sun's rays pass through a deep layer of fog or through ordinary window glass, much of the ultraviolet radiation is lost, and thus also the power to synthesize vitamin D.

An important source of vitamin D for man is his food. It is present in large amounts in the liver oil of certain kinds of fish, and in much smaller quantities in milk, butter, cheese, eggs, and fat fish (herring, salmon, sardines). The fat of fish contains much vitamin D, that of other animals little or none, unless they feed on fish. The vitamin-D content of liver oil and of the foodstuffs mentioned shows wide variations, depending on a number of factors. The greatest differences depend on the season of the year. Thus milk and its products and eggs obtained in summer contain far more vitamin D than in winter.

Here a reminder should be given that nowadays margarine is often used as a butter substitute, and that this product does not contain vitamin D unless it has been specially added. It should also be pointed out that the regular internal use of liquid paraffin may lead to a disturbance of vitamin-D absorption, the vitamin being taken up by the paraffin.

Calcium Depletion

As vitamin-D deficiency is often due to a shortage of milk products, the nutrition is also deficient in calcium. Even so, this need not lead to the development of frank osteomalacia so long as the subject is exposed to a sufficiency of sunlight. Hence it is that the disease is most often seen in those who lead mainly an indoor life.

The risk of osteomalacia developing is greater when the vitamin-D deficiency is accompanied by some other condition—for example, pregnancy—promoting calcium depletion. In the last stages of pregnancy the mother loses 20–30 g. of calcium to the foetus, and during lactation there is a daily loss of 250–350 mg. of

calcium in the maternal milk. Moreover, during pregnancy the *p*H of the gastric juice is often high, and this exerts an unfavourable influence on calcium absorption from the intestine. Although "hunger osteomalacia" occurs only rarely, mild forms of the disease have been observed in pregnant women and, according to Meulengracht, also in the elderly.

Faulty Intestinal Absorption

An important cause of osteomalacia is a disturbance of absorption of vitamin D by the intestine, which is usually accompanied by a disturbed calcium absorption. Vitamin-D absorption takes place in the small intestine, the presence of bile being necessary even though there is an excess of the vitamin. Hence absorption is inadequate when there are biliary fistulae, and in cases of prolonged jaundice due to biliary congestion or liver disease. Sprue or chronic pancreatitis is more often the cause, in which vitamin D as well as vitamins A and K (the fat-soluble vitamins), but also calcium, are insufficiently absorbed. Lastly, in regional ileitis and after operations in which an intestinal shunt has been made the absorption of vitamin D may be inadequate.

Lack of calcium may be due to the formation in the bowel of insoluble calcium complexes (oxalate, and particularly phytate). The latter is found in large amounts in cereal grains.

Skeletal Abnormalities

It is worthy of note that in the clinical picture of osteomalacia as sometimes observed it is not so much the skeletal deformities caused by the calcium deficiency (thin, flexible cortex of long bones, deformed pelvis, and "fish vertebrae" due to pressure of the intervertebral disks) which dominate the picture, but rather more local abnormalities with more or less (and not rarely very little) decalcification. This is to be attributed to the shorter duration of the process (Dent and Hodson, 1954). It should be realized that radiologically visible general skeletal abnormalities do not arise until after the calcium reserve has decreased by about 30%. The abnormalities are then limited to slit-like or wider (band-shaped) clear areas in the skeletal shadow. Usually there are several at the same time, in most cases localized symmetrically. These gaps may be shallow, but they may also interrupt the whole continuity of the skeleton (pseudo-fissures or pseudo-fractures). They are especially to be found in the os pubis and ischii, collum femoris, the ribs, radii, ulnae, and metatarsals. Looser (1920), who extensively studied these abnormalities in patients suffering from osteomalacia and rickets, called them *Umbauzonen* (zones of transformation) because they are not real fractures. Histological examination proved them to consist of non-calcified cells, which was confirmed by Seeliger (1923) and Justin-Besançon, and Delarue.

In the literature these radiological abnormalities are sometimes referred to as the "Milkman syndrome." They occur, however, especially in osteomalacia due to vitamin-D deficiency or disturbed renal tubular function (renal tubular osteomalacia; see below). They are sometimes also observed in other skeletal diseases (Paget's disease, Cushing's disease, congenital syphilis, hyperparathyroidism), but in such cases they are not symmetrically localized, which is usually the case in osteomalacia (Albright). Moreover, these *Umbauzonen* develop at sites where osseous abnormalities were already present, or as a result of trauma (Steinbach *et al.*, 1954).

These skeletal abnormalities and the above-mentioned localization were initially attributed (Looser, 1920; Justin-Besançon, 1942; Debray *et al.*, 1943; Boquien and Bureau, 1943; Pompen *et al.*, 1946) to the association of decalcification with "mechanical stress" to which these parts of the skeleton were especially exposed. Recently, on the basis of anatomical (Le May and Blunt, 1949) and angiographic research (Steinbach *et al.*, 1954), it has been sought to establish a relationship with the locally close contact of pulsating blood vessels with these bones, and thus introduce the concept of "vascular stress."

It may here be of interest to present some examples of these skeletal abnormalities observed in patients with osteomalacia caused by deficient nutrition during the war years 1943–5. The patients were nuns living in convents, 15 of whom showed the same signs and symptoms. In these cases lack of solar radiation was probably an additional factor. The patients complained of pains in the loins and upper legs, with difficulty in rising from the sitting position. They had a tottering gait, and often were unable to lift their legs adequately during walking. It is important to remember that these patients are usually not emaciated, as it is the quality rather than the quantity of their food which is at fault. Both the inorganic phosphate and calcium levels of the serum may be decreased, though it is not unusual for normal values to be found, as in our patients; the alkaline phosphatase level is increased, however (Table I).

TABLE I.—*Laboratory Findings and Skeletal Lesions in Patients with Osteomalacia Due to Nutritional Deficiency*

Patient	Age (Years)	Serum			E.S.R. (mm. in 1 hr.)	Haemoglobin (%)	Achylia Gastrica	Pseudofractures
		Calcium (mg./100 ml.)	Phosphorus (mg./100 ml.)	Alkaline Phosphatase (K.-A. units)				
M.	54	11	4·2	17·4	20	80	+	Os pubis
H.	38				14			" (bilateral)
H. after treatment	39	9·7	4·3	5·5				Coll. femoris
P.	48	11	3·8	21·7	12	77	+	Os pubis, os ischii (bilateral)
A.	37	10·2	2·4	11·2	15			Os ischii (bilateral)

On the radiographs clear *Umbauzonen* are visible in the pelvis and femoral neck (Special Plate, Figs. 1 and 2). Similar radiological abnormalities are found in non-tropical sprue, a case of which is illustrated in Figs. 3A and 3B of the Special Plate. This patient had low levels of calcium (7 mg. per 100 ml.) and inorganic phosphate (2.1 mg. per 100 ml.), with increased alkaline phosphatase (21.4 King–Armstrong units) and low excretion of calcium in the urine. The deterioration in her condition during the period 1951–6, when she had withdrawn from treatment, is clearly visible.

While it is true that to-day the forms of osteomalacia which are due to deficient nutrition or disturbed absorption are not very prevalent in Western Europe, the possibility of their occurrence should not be overlooked. A satisfactory body weight certainly does not exclude this pathogenesis, as the deficiency in question is usually qualitative rather than quantitative.

The *x*-ray abnormalities described above may also occur in the absence of nutritional deficiency or disturbed absorption in the small intestine, and the causes of this deserve mention.

Non-nutritional Causes

Renal Tubular Dysfunction

A disturbance of renal tubular function, with insufficient reabsorption of inorganic phosphate, may give rise to the same picture. Concentration by the kidney is normal, and so is glomerular function. In these patients absorption of calcium from the intestine is also disturbed, urinary calcium excretion being low (Snapper, 1957). Serum calcium is normal, inorganic phosphate decreased, and alkaline phosphatase increased. Excretion of inorganic phosphate in the urine is not remarkably high, but high enough when compared with the low serum level. As this form of osteomalacia does not react to vitamin-D treatment it is sometimes referred to as vitamin-D-resistant osteomalacia. In this disease the radiological abnormalities (*Umbauzonen*) already described have repeatedly been found. It may occur in a milder form, so that the patient reaches adult age before it is discovered, but often such patients have already suffered from rickets in their youth as a manifestation of the underlying metabolic upset (Anderson *et al.*, 1952).

In addition to the disturbance of inorganic phosphate reabsorption, the reabsorption of glucose (renal glycosuria) and/or amino-acids (aminoaciduria) may also be affected; in the latter case sometimes of only one amino-acid—namely, glycine (Rose, 1956). When the picture is one of aminoaciduria it is called Lignac–De Toni–Debré–Fanconi syndrome. Sometimes the disease is not of a hereditary nature, and the radiological and biochemical manifestations of osteomalacia do not appear until the age of 16 years or more.

Inability of Renal Tubules to Produce Acid Urine, Combined with Disturbed Formation of Ammonia, Causing Acidosis

As a compensatory mechanism in this disorder sodium, potassium, and calcium are utilized as bases for the excretion of the acid radicals. The increased excretion of calcium and phosphate brought about in this way causes osteomalacia. This picture is observed in cases with congenital dysfunction of the distal convoluted tubules or chronic pyelonephritis, and also after administration of large doses of sulphanilamide (Snapper, 1949).

Idiopathic Hypercalciuria

This abnormality is caused by disturbed tubular reabsorption of calcium, so that much calcium is excreted in the urine and nephrolithiasis develops (Klotz *et al.*, 1955). An opportunity has recently arisen to study this condition in a 15-year-old boy who came under treatment for attacks of abdominal pain and haematuria.

On a diet containing 280 mg. of calcium a day the 24-hour urinary calcium excretion was 317 mg. Calcium was deposited in several renal calices (Special Plate, Fig. 4). The calcium and inorganic phosphate levels were normal (9.9 and 2.5 mg. per 100 ml. respectively), but alkaline phosphatase was increased (19 King–Armstrong units). No skeletal defects were demonstrable radiologically. Renal function was normal (phenolsulphonphthalein test (Rowntree) 70%; urea clearance 60%), as also was the alkali reserve of the blood (48.3 vols.%).

In addition to those mentioned above there are other, rarer, causes of osteomalacia—for example, disturbed formation of alkaline phosphatase by the osteoblasts—which cannot be dealt with here.

Prolonged Corticosteroid Treatment

Marked osteoporosis, and also osteomalacia, may develop after prolonged treatment with corticotrophin or cortisone, as we have recently observed in several cases.

One patient, a 53-year-old man with rheumatoid arthritis, had been treated for three years successively with corticotrophin, cortisone, and (for the last year) 15–25 mg. prednisone per day. *X*-ray examination showed marked atrophy and decalcification of the skeleton, in particular of vertebrae, one of which showed a fracture with wedge-shaped compression (Special Plate, Fig. 5). The serum calcium was 9 mg. per 100 ml., inorganic phosphate 3.2 mg. per 100 ml., and alkaline phosphatase 15 King–Armstrong units. After loading with 945 mg. calcium (according to Nordin and Fraser, 1956; see below) the four-hourly retention was 78.3% and the 12-hourly excretion only 16.7%. The picture is therefore characteristic of osteomalacia.

In recent years several cases of osteoporosis with fractures (of vertebrae, femoral neck, ribs, pelvis) have been described in patients treated with cortisone or corticotrophin for rheumatoid arthritis, pemphigus, bronchial asthma, or lupus erythematosus (Curtiss *et al.*, 1954; Turiaf *et al.*, 1956; Vignon *et al.*, 1956). The fractures sometimes occurred as early as two months after treatment was started, and in such cases the previous condition of the skeleton and the dosage of corticosteroids play their part. The cause of these skeletal abnormalities can be sought in antianabolic influences involving the proteins. Not only does urinary nitrogen excretion increase as a result of hormonal treatment, but also the excretion of calcium (Sprague *et al.*, 1950; Eliel and Heaney, 1954; Luft *et al.*, 1954) and phosphate (Roberts and Randall, 1955). Of great importance is the considerable loss of calcium in the stools (Sprague *et al.*, 1950; Anderson *et al.*, 1952; Lichtwitz *et al.*, 1955; Morgan *et al.*, 1956). It is probable that this is due to an increased excretion via the intestines (Morgan *et al.*; Lichtwitz *et al.*) rather than to decreased absorption (Anderson *et al.*). The possibility that osteomalacia may also develop must therefore be reckoned with. Support for this opinion was provided by the fact that our patient had an increased blood alkaline phosphatase, and also by the result of the calcium loading test, in which calcium retention was 78%. On the other hand, the blood alkaline phosphatase might not be increased, any tendency for it to rise being controlled by the corticotrophin (Bardawill *et al.*, 1951). In our patient the alkaline phosphatase level rose after discontinuation of treatment.

An increased serum alkaline phosphatase has also been found in cases of Cushing's syndrome. As the mechanisms of action of the glucocorticoids are many the effect on the skeleton will depend on which of these mechanisms predominates. If the loss of calcium in the stools (due to the increased excretion) preponderates over the anti-anabolic action on the osteoid tissue a picture of osteomalacia will arise. In most cases, however, the anti-anabolic action probably predominates, so that the resultant picture is one of osteoporosis.

Diagnosis

A differentiation must be made between osteomalacia and osteoporosis; in the latter the growth of the bone matrix is disturbed, so that there are no osteoid zones. This is one of the possibilities to be kept in mind when dealing with menopausal women. It is not always easy

to distinguish between osteoporosis and osteomalacia. Not infrequently causes for both affections may be present—for instance, after prolonged treatment with corticotrophin or cortisone. When nutrition is inadequate there are often multiple deficiencies. In the elderly a deficiency of vitamin D and of calcium may occur: protein depletion is also a possibility. So that suitable treatment may be instituted it is necessary to determine which processes are responsible for the faulty calcification of the skeleton. In typical osteoporosis the decalcification is rarely localized in the long bones, and the plasma concentrations of calcium, phosphate, and alkaline phosphatase are normal.

Early diagnosis is most important. Although increase in alkaline phosphatase occurs early in osteomalacia, it is not pathognomonic for this disease. One of the earliest manifestations is atrophy, in the form of a thinning of the cortex, of the bones of the hand; the other radiological abnormalities of the skeleton occur only later.

Finlay *et al.* (1956) have recently described some useful diagnostic tests. These are based on the fact that, after intravenous infusion of calcium in osteomalacia, the calcium rapidly disappears from the blood, while only small amounts are excreted in the urine. In osteoporosis the calcium disappears more slowly from the blood and is excreted in the urine in normal quantities. In osteomalacia from 62% to 88% of the calcium injected is retained, while in osteoporosis retention is normal (50% to 62%) or even below normal. We have applied these tests in a number of cases, and the results are shown in Table II. From

TABLE II.—*Results of Calcium Infusion Tests*

	Serum			Calcium Infusion Test (Finlay, Nordin, and Fraser)		
	Calcium (mg./100 ml.)	Phosphorus (mg./100 ml.)	Alkaline Phosphatase (K.-A. Units)	Serum Calcium after Infusion (mg./100 ml.)	12-hour Excretion in Urine (%)	4-hour Skeletal Retention (%)
Normal	9–11	2·5–3·5	<10		33–53	50–62
Sprue:						
Patient J.	6·0	2·1	21·4	8·3	3·8	73·9
,, B.	8·6	3·5		9·7	2·0	87·3
Idiopathic hypercalciuria	9·9	2·5	19·0	11·3	17·4	71·0
Prolonged steroid treatment (vertebral fracture)	9·0	3·2	15·0	10·2	16·7	78·3
Osteoporosis:						
Patient R., 84 yrs.; senile	10·6	2·8	7·9	15·3	43·6	25·0
,, L.; immobile ..	10·6	3·0	5·0	16·3	28·8	31·4
,, S.; neurofibromatosis ..	10·3	2·5	7·0	14·1	36·8	39·1
,, B., 66 yrs.; senile	9·5	2·5	9·0	14·2	26·6	45·1

this it may be seen that calcium retention in the two patients with osteomalacia in non-tropical sprue was 73.9% and 87.3% respectively. The case of primary hypercalciuria, in which radiological abnormalities of the skeleton had not yet developed, had a calcium retention of 71%. In the case with marked decalcification after prolonged treatment with corticotrophin, cortisone, and prednisone, the calcium retention was 78%.

Treatment

The various forms of osteomalacia described above require greatly different treatment. In vitamin-D deficiency it is evident that this vitamin should be administered, but the dosage varies with individual patients between 2,000 and 10,000 i.u. per day. The patient's reaction must therefore be studied. If treatment is adequate some relief of pain is usually obtainable within a few weeks, but it may be several months before clinical cure can be expected.

Vitamin D can be given as such or in the form of cod-liver oil. An ample supply of calcium is also necessary—for example, by the consumption of at least 1–1.5 litres of milk per day. When there is a disturbance of absorption this should be treated; but this subject cannot be entered into here other than to point to the great advances made in the treatment of non-tropical sprue by the prescription of a gluten-free diet, as witness the excellent results obtained by Weyers and van de Kamer in coeliac disease. The diet should not contain wheat, rye, or oats, therefore bread made from these cereals should not be eaten; gluten-free bread—for example, prepared from buckwheat—or Liga wheat-free cakes are, however, allowable. We usually give two hot meals a day from which macaroni, spaghetti, vermicelli, sausage, etc., are excluded. Rice and buckwheat are allowed. We have obtained very favourable results with this regimen in adults, the stools becoming practically normal and with a much reduced fat content. To combat the osteomalacia vitamin D is given, usually in the form of 10,000–25,000 i.u. of calciferol. If the defective absorption persists, then a single injection of vitamin D in massive dosage (500,000 i.u.) may be given. Total body irradiation with ultraviolet light is of great use.

In renal tubular osteomalacia results can be obtained only with massive doses (400,000–600,000 i.u.) of vitamin D; hence the name vitamin-resistant osteomalacia. In this connexion it should be borne in mind that, although these cases are resistant to vitamin D in therapeutic dosage, large doses may still produce toxic effects. Thus the gap between toxic and therapeutic doses is small. It is therefore advisable to start with 50,000 i.u. per day and gradually increase the dosage until the blood phosphate level has risen to 2.5–3 mg. per 100 ml. Efforts should then be made to find the minimum maintenance dose. Sometimes a dosage of 200,000–400,000 i.u., equivalent to 5–10 mg. calciferol, is necessary, but this may give rise to toxic manifestations. The patient should therefore be carefully observed; as soon as he complains of nausea, vomiting, or polydipsia or polyuria, treatment must be stopped and an extensive clinical examination carried out. Vitamin-D intoxication will be referred to later.

Rose (1956) and others have reported very good results with "A.T.10" (dihydrotachysterol) in patients with "resistant osteomalacia." The patients recovered, the plasma phosphate and alkaline phosphatase levels returned to normal, calcium balance became positive (the calcium content of the faeces falling considerably), and the osteoid zones of the bony skeleton became calcified. These authors are therefore of the opinion that A.T.10 exerts an excellent antirachitic action in the human subject. In Rose's case of renal tubular osteomalacia the dosage was 5 mg. pure dihydrotachysterol per day for 13 days, then 2.5 mg. for 10 days, and finally a maintenance dose of 1.5–1.25 mg. (=0.3–0.25 ml. of the oily solution).

Dent and Harris (1956) advise that treatment should be withheld in mild cases, such as are occasionally found among the relatives of patients with more severe disease, unless suspicious symptoms appear. The patient observed by McCance (1947), after treatment with a high dosage of vitamin D, continued in good health without further treatment (Dent and Harris, 1956).

In patients with renal tubular osteomalacia and acidosis the latter must be treated with a mixture of citric acid and sodium citrate—for example, 120 ml. per day of a solution containing 16 g. citric acid and 12 g. sodium citrate. In each case, however, the dosage must be designed to promote a rise in alkali reserve to 50–60 vol.% (bicarbonate level 25–27 mEq/l.). In these cases account has to be taken of the fact that the hypopotassaemia is usually more severe than the hypocalcaemia.

In idiopathic hypercalciuria the deficiency is not of vitamin D but of calcium, so that 1–1.5 litres of milk per day with calcium in the form of the lactate or gluconate (5–10 g. per day) is to be recommended. Klotz *et al.* (1955) recommend testosterone, which Selye maintains will increase the reabsorption of calcium, and Klotz *et al.* themselves consider will promote in addition "la meilleure fixation osseuse du calcium."

Prophylaxis

Prophylaxis should be considered in all cases of sprue, and of chronic pancreatitis, and in pregnancy and adolescence. In the last two categories, and in women during lactation, it is beneficial to give, for example, 800–1,000 i.u. of vitamin D per day together with ample calcium in the form of milk (0.75–1 litre per day). Patients suffering from sprue should also be given calcium in the form of milk, and, if desired, calcium gluconate with 4,000 i.u. of vitamin D per day.

With respect to this measure it should be emphasized that (1) vitamin-D requirements show great individual differences; and (2) an excess of vitamin D may give rise to toxic manifestations. The vitamin-D requirement depends on the following factors: (1) Age (growth rate). (2) The degree of exposure to sunlight (ultra-violet rays). The formation of vitamin D in the skin under the influence of sunlight likewise shows individual variations; there probably exists a relationship between this form of vitamin-D production and the colour of the skin. (3) The calcium–phosphate ratio in the diet. This ratio seems to be more favourable in human than in cow's milk, so that serious forms of rickets are only rarely observed in breast-fed children, in contrast to those who receive an excess of cow's milk. (4) Heredity also has an important bearing on the vitamin-D requirement. This does not come into play when the diet is adequate, but when the vitamin content falls to the limit of what is necessary deficiency symptoms are likely to develop in those whose vitamin-D requirement is above the average. The genetic factor is especially important at the present day, with the great improvement in nutrition that has taken place (Dent and Harris, 1956). (5) It should also be kept in mind that in certain diseases, such as sarcoidosis (Anderson *et al.*, 1954), there exists an increased sensitivity to vitamin D.

Vitamin-D Intoxication

When vitamin-D therapy is under consideration due attention should be paid to the probable toxic effects of overdosage. It is impossible to define what is a toxic dose of the vitamin, because of individual differences in sensitivity, and therefore it is important to recognize the signs and symptoms of intoxication. These are usually anorexia, nausea, vomiting, and especially polyuria and polydipsia.

It is generally held that a rise in blood calcium level is an indication of toxicity, but when this occurs there probably already exists a severe form of intoxication. In an experimental investigation in our laboratory Takens (1956) observed that, after moderate doses of calciferol had been given to rats and rabbits, a significant increase in urinary calcium excretion occurred as compared with a control series, while the blood calcium level remained normal (Tables III and IV).

TABLE III.—*Diuresis, Serum Calcium Level, and Urinary Calcium Excretion in Rats Given* 20,000 *i.u. Calciferol per kg. Daily*

Days Before (−) and After (+) Start of Calciferol Administration	Urine (ml./24 hours)			Serum Calcium (mg./100 ml.)		Urinary Calcium (mg./24 hours)		
	Rats Given Calciferol		Controls	Rats Given Calciferol	Controls	Rats Given Calciferol		Controls
	1–4	5–8	9–12			1–4	5–8	9–12
− 7	29	31	28					
− 1	24	29	32	8·5–10·2	8·9–10·4	4·7	4·8	5·4
+ 14	32	41	28					
+ 21	54	62	22	8·6–10·5	9·4–10·7	16·4	17·9	5·4
+ 28	30	38	28					
+ 35	52	61	31			17·4	17·8	7·9
+ 42	32	43	34	9·8–12·5	9·2–10·4			
+ 49	58	63	33			19·7	18·8	8·3
+ 56	66	60	21	8·6–11·3				
+ 85	62	98	26	10 –11·1		21·2	28·4	6·6
+ 99	75	79	35					
+113	83	71	20	10·6–11	8·9–10·1			

TABLE IV.—*Urinary Calcium Excretion in Rabbits Given* 20,000 *i.u. Calciferol per kg. Daily*

Days Before (−) and After (+) Start of Calciferol Administration	Calcium Excretion (mg./24 hours)			Days Before (−) and After (+) Start of Calciferol Administration	Calcium Excretion (mg. 24 hours)		
	Rabbits Given Calciferol		Control		Rabbits Given Calciferol		Control
	1	2			3	4	
−19	5·6	9·8	14·4	−26	16·7	16·2	34·5
− 5	16·7	29·1	6·6	−12	22·0	10·6	15·3
+ 9	67·7	70·8	16·5	+ 2	15·8	16·2	9·5
+23	32·5	64·0	10·7	+16	76·1	294·0	8·6
+37	179·8	241·1	14·3	+30	211·4	158·9	16·6
+51	248·9	218·1	6·9	+44	203·6	135·2	12·1
				+58	179·9	133·5	13·5

Moreover, in the rats, which were allowed unlimited quantities of distilled water, a marked polydipsia and polyuria developed. The increased calcium excretion was not such that the polyuria could be attributed to it (osmotic diuresis), more especially as the rabbits, which apart from their food were not given fluids, had an increased calcium excretion but no polyuria. A rise in blood calcium is probably a much more serious sign of intoxication. We were also able to observe clinically that the Sulkowitch test became positive before the blood calcium level rose.

In order to diagnose incipient vitamin-D intoxication, therefore, it is necessary to check the diuresis and the urinary calcium excretion. An increase of the latter indicates intoxication even if the blood calcium is still normal.

Summary

The cause of osteomalacia may be of widely varying nature: in the first place vitamin-D deficiency, which may be the result of deficient nutrition, and secondly insufficient absorption of vitamin D from the intestine (non-tropical sprue, chronic pancreatitis, etc.). In these cases the absorption is usually also deficient as regards calcium. At present the picture of classical osteomalacia with marked skeletal deformation is only rarely observed in Western countries, but milder forms are not rare. Although the general nutrition is good because a sufficient number of calories is taken up, the qualitative composition of the diet does not always come up to the standard required. The development of osteomalacia is further promoted by a lack of sunshine or by pregnancies. In these cases Looser's *Umbauzonen* (Milkman's syndrome) are often observed.

It is also of importance to know that these syndromes may be caused by diseases of the kidney such as renal tubular osteomalacia (vitamin-D-resistant osteomalacia), renal acidosis, and idiopathic hypercalciuria. Prolonged treatment with corticotrophin and cortisone may cause not only osteoporosis, but also osteomalacia. The calcium loading test is of great value in the differentiation between osteoporosis and osteomalacia.

The various causes of osteomalacia should be taken into account if rational treatment is to be given. A diet rich not only in vitamin D but also calcium (milk and buttermilk) is indicated in vitamin-D deficiency, or in the case of deficient absorption. Gluten-free food is of importance in non-tropical sprue. "A.T.10" has proved to be of great value in renal tubular osteomalacia.

Prophylactic treatment with vitamin D and calcium is recommended in all cases of non-tropical sprue and of chronic pancreatitis, and in pregnancy.

With vitamin-D treatment care should always be taken to avoid vitamin-D intoxication. Constant attention should therefore be given to the initial manifestations of this condition, among which are polyuria, polydipsia, anorexia, and vomiting. Investigations in our clinic have shown that, in combination with polyuria, an increase in urinary calcium excretion probably occurs even before a rise in blood calcium level is observed.

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SURGICAL DIAGNOSIS OF "CHRONIC PANCREATITIS" AND CHRONIC RELAPSING PANCREATITIS

BY

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[WITH SPECIAL PLATE]

In this paper are reviewed 22 cases in which the presence of non-malignant chronic pancreatic disease has been apparently confirmed during operation. A number of these patients, in whom a histological diagnosis of "chronic pancreatitis" was made on surgical biopsy material, died later from pancreatic carcinoma. This suggests that misinterpretation of the essential underlying pathology in patients with chronic pancreatic disease may occur frequently, and justifies publication of an analysis of the principal clinical and morbid anatomical findings in the present cases.

The 22 patients under review underwent in-patient treatment at St. Bartholomew's Hospital between 1941 and 1956, and were selected from among the 39 patients with a diagnosis of either chronic pancreatitis or chronic relapsing pancreatitis recorded by the Department of Medical Statistics during this period. Of the 17 patients excluded, 12 were not subjected to laparotomy, and thus the diagnosis cannot be considered to have been established; and in five cases it appears in retrospect that the operative findings were insufficient to support the diagnosis in the absence of pancreatic biopsy material. The records of the remaining patients have been perused and information about those still living has been obtained by letter; all available morbid anatomical material and the radiographs have been re-examined.

The clinical course of these 22 cases allows their separation into two groups. Group I consists of 12 patients in whom a diagnosis of "chronic pancreatitis" was made upon the operative findings, supplemented in most cases by examination of surgical biopsy material, and who died within three years of operation. Group II includes the remaining 10 patients, in whom the clinical picture supported a diagnosis of chronic relapsing pancreatitis and all of whom survived operation for a period varying from six to 40 years.

Group I: Diagnosis of "Chronic Pancreatitis," followed by Death within Three Years of Operation

Clinical Features

The group comprised 11 males and one female. The age of onset of symptoms referable to the local condition varied between 41 and 82 years, with an

average of 59 years. Jaundice of obstructive type was present in 10 patients, in all of whom it formed the main indication for surgical exploration. In the other two patients this sign was absent; they had presented with a palpable abdominal tumour and duodenal obstruction, respectively. Pain was recorded in the history of six cases, but in no case did it form the presenting symptom, nor did its relief constitute an indication for surgical treatment.

Nine cases were explored in the presence of jaundice, and a further case gave a recent history of transient icterus. The duration of this symptom before operation varied between 2 and 18 weeks, the average being 7.6 weeks. A palpable gall-bladder was recorded in only three of the patients with jaundice. The serum bilirubin was estimated in nine cases; the highest recorded levels varied between 1.5 and 21.6 mg. per 100 ml., with an average of 11.2 mg. In all these cases the direct van den Bergh reaction was obtained.

The period of survival after exploration varied between four days and three years and averaged eight months. Eight patients died within the first four months after operation, and only two survived more than one year.

Radiological Findings

Not all the patients in Group I underwent full radiological investigation, and, since the majority gave a history of recent jaundice, cholecystography revealed little useful information. However, plain radiographs of the abdomen were available in all cases and a barium-meal examination was carried out in seven cases. The results of these investigations are given in Table I. No calcification in the region of the pancreas

TABLE I.—*Radiological Findings in Groups I and II*

	Group I (No. of Cases)	Group II (No. of Cases)
Pancreatic calcification:		
Present	0	4
Absent	12	6
No investigation	0	0
Total	12	10
Changes in appearance of duodenal loop:		
Present	1	5
Absent	6	1
No investigation	5	4
Total	12	10

was seen in any patient in Group I. In one instance the barium meal revealed distortion of the pyloric region and second part of the duodenum; these changes coincided with a palpable mass and were considered to be consistent with a diagnosis of pancreatic carcinoma in this case.

Operative Findings

The principal operative findings are shown in Table II; the macroscopical appearance of the pancreas is described in further detail below under "Pathological Findings."

In all 12 cases in Group I the pancreas was obviously the seat of disease, and appeared to be responsible for the biliary obstruction in the jaundiced patients. In these exploration confirmed that the common bile duct and gall-bladder were dilated. No gall-stones were encountered in any patient in this group. Nevertheless, in most cases it proved difficult or impossible for the surgeon to determine whether the pathological condition in the pancreas was malignant or benign. Further information was sought by biopsy examination of a

TABLE II.—*Operative Findings*

Findings	Group I (No. of Cases)	Group II (No. of Cases)
Dilatation of common bile duct	10	3
Normal common bile duct	2	7
Total	12	10
Mass in head of pancreas	7	1
Mass in body of pancreas	2	0
Uniform hardness and irregularity	3	4
Subacute pancreatitis	0	3
No record	0	2
Total	12	10
"Cysts"	2	2

small piece of tissue removed from the surface of the pancreas. The final diagnosis of "chronic pancreatitis" was made by the surgeon, after consideration of the clinical and pathological evidence available at the time.

In the 10 patients with jaundice surgical procedures were undertaken to relieve the biliary obstruction by internal drainage. The remaining two patients underwent no further surgical intervention.

Pathological Findings

Macroscopical. — The pathological diagnosis of "chronic pancreatitis" was made upon the findings at operation. With two exceptions, patients were explored because they were suffering from obstructive jaundice of recent onset. Careful examination of the pancreas and biliary passages by the surgeon was supplemented by a surgical biopsy in eight cases. The principal operative findings are given in Table I. A mass was present within the pancreas in nine cases, being situated in the head of the organ in seven and in the body in two. A uniform hardness, nodularity, or irregularity of the pancreas was found in three cases. Cysts were encountered in the body and tail of the pancreas in two cases. These contained turbid, mucinous fluid, and in one case were as large as 1 in. (2.5 cm.) in diameter. Reference to this finding as a possible indication of pancreatic ductal obstruction will be made later.

Biopsy.—The surgical biopsy material reveals a number of histological similarities (Special Plate, Figs. 1 and 2). The predominant feature is fibrous replacement of the pancreatic parenchyma. The acini show a variable degree of atrophy, and in some cases have completely disappeared. The small pancreatic ducts in some sections show proliferative changes, but in the cases in which advanced fibrosis is present only a few ductal remnants are seen. The islets of Langerhans appear slightly reduced, but in some specimens can be clearly identified, where disappearance of the ductal and acinar structures has removed all other trace of the tissue of origin. The specimens show a variable degree of infiltration with lymphocytes and plasma cells, and scattered lymphoid follicles are occasionally present.

Necropsy.—A full post-mortem examination was made in five cases. A carcinoma of the head of the pancreas was present in four, and in the remaining case the head and body of the organ contained large metastases from a primary bronchial carcinoma. Three organs showed marked distension of the pancreatic ductal system. The irregular dilatation of the ducts, filled with a mucinous material, produced a cystic appearance, the true nature of which had not been appreciated at the time of operation, although note was made of the presence of "cysts" in two instances. The

dilatation involved the main pancreatic duct, and to a less extent its secondary tributaries, in the parts of the pancreas caudal to the malignant process.

Histological examination of the necropsy material confirmed involvement of the pancreas by a primary adenocarcinoma in three cases and by mucoid carcinoma in one; the fifth pancreas contained oat-celled carcinoma, the primary source being in the left main bronchus. Microscopical examination of the parenchyma, apart from the regions directly infiltrated by the neoplasm, revealed a combination of acinar replacement fibrosis, minor ductal hyperplasia, and infiltration with chronic inflammatory cells. These changes showed some variation in different parts of the same specimen. In three instances it was possible to compare the histological appearances at necropsy with those of the surgical biopsy specimens obtained earlier in the course of the disease. Apart from the fact that the necropsy specimens showed widespread involvement by neoplastic tissue, not recognizable in the biopsy material, there was no essential difference in either the type or degree of the accompanying changes in the parenchyma.

Group II: Chronic Relapsing Pancreatitis

Clinical Features

The group consisted of those patients with chronic disease of the pancreas, confirmed by laparotomy, in whom the clinical picture supported a diagnosis of chronic relapsing pancreatitis and who remained alive more than three years after exploration. As the number of cases (seven males and three females) is too small to justify an exhaustive review the principal clinical features only will be presented.

The age of onset of abdominal symptoms varied widely. The youngest patient began to have typical attacks of pain at the age of 18, but gave a history of abdominal pain since early childhood; the oldest patient had the first attack at 65 years of age. The average age of onset in the group was 45 years. The chronicity of the disease is indicated by the period which elapsed between the onset of symptoms and abdominal exploration. This was 14 years in two cases, and was less than two years in only one case, in marked contrast to the short clinical course of the symptoms in Group I. When the period of survival after exploration is considered it is found that only two patients had died at the time of review, respectively nine and 40 years after operation. The follow-up period in the rest of the group varied between five and 10 years after surgery, and the average in the whole group was 11 years. The justification for considering cases of chronic relapsing pancreatitis in a separate group from patients with "chronic pancreatitis" dying within three years is strongly supported by an entirely different clinical picture in the two groups.

Attacks of abdominal pain have been the principal feature in all cases in this group, and have also been the initial symptom in the disease. In most cases the first attack was not the most severe, but was followed after a period of months or years by similar episodes, often becoming progressive in severity and frequency. The character and site of the pain were constant. It occurred in the right hypochondrium and epigastrium, seldom well localized, and was invariably accompanied by radiation to the middle of the back or to one or both loins.

Obstructive jaundice had occurred at one time or another in five cases. The obstruction was transient, so that no patient was operated upon in the presence of jaundice. For this reason the recorded levels of serum bilirubin in this group give little indication of the severity of the biliary obstruction, since the investigation was carried out after admission to hospital, usually several weeks after complete subsidence of the icterus. Thus one patient gave a clear history of jaundice accompanying an abdominal episode six years before operation, when the serum bilirubin was normal. In spite of this, when the highest recorded bilirubin levels are considered in the three patients who had transient jaundice less than six months prior to operation, these levels on admission were between 2.5 and 12.0 mg. per 100 ml. A direct van den Bergh reaction was present in all of these. With one exception, the jaundice in these five cases accompanied a clinical attack of pancreatitis in which pain was the predominant symptom.

Vomiting was a feature in five cases, in two of which it was severe, resembling that seen in pyloric obstruction. In one of these cases operation was undertaken principally with the intention of relieving this symptom. Disturbance of bowel function and the passage of frequent loose stools occurred in only two cases. It may be mentioned that these were the only cases in which significant psychological abnormality appeared to be present, and that these patients both underwent splanchnic nerve section without any definite permanent relief of abdominal pain. Three patients developed diabetes mellitus during the course of the disease, and investigation revealed a diabetic type of dextrose tolerance curve in a further case. A significant history of alcoholism was not manifest in any of the patients under review.

In some instances a raised serum amylase level was recorded during the acute exacerbations of the disease. Although this may be taken as confirmatory evidence of parenchymal involvement during the episodes of pancreatitis, the investigation was not used universally.

Radiological Findings

Table I indicates the results of radiological investigation in the two groups. Plain films of the abdomen were available in all the cases of chronic relapsing pancreatitis, and four of these showed obvious opacities in the region of the pancreas. The calcification varied in distribution and intensity, but was very pronounced in two cases (Special Plate, Fig. 3). There was no visible calcification at the time of examination in the remaining six cases.

A barium-meal examination was carried out in six cases in Group II, and in five of these abnormal changes in the region of the duodenal loop were demonstrated (Special Plate, Fig. 4). Thus, apparent flattening of the lumen in the second and third parts of the duodenum was reported in three cases and widening of the duodenal loop in two. In one case there was thickening of the mucosal folds of the duodenum and duodeno-jejunal flexure associated with apparent irritability of the second part of the duodenum and widening of the loop. Other changes seen in the patients in this group were displacement of the body of the stomach in one case, and of the duodeno-jejunal flexure in another. These radiological appearances indicated that the head of the pancreas was enlarged in three of the cases and the body in two. In the sixth

F. S. P. VAN BUCHEM: OSTEOMALACIA

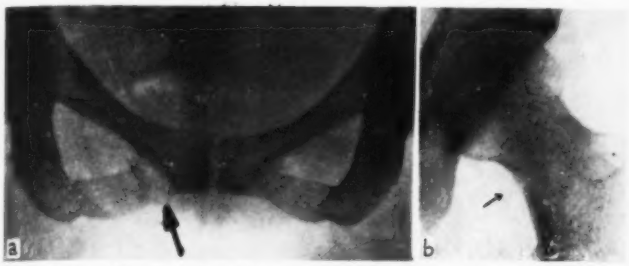

FIG. 1.—Case H. Transformation zones: (*a*) os pubis; (*b*) collum femoris.

FIG. 2.—Case P. Three transformation zones.

FIG. 3A.—Case J. (sprue). 1951: one transformation zone.

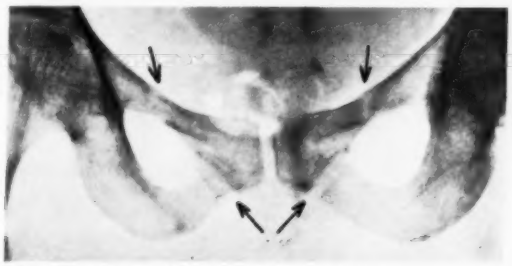

FIG. 3B.—Case J. 1956: four transformation zones; general decalcification.

FIG. 4.—Idiopathic hypercalciuria. Intravenous pyelogram showing calcium deposition in several renal calices.

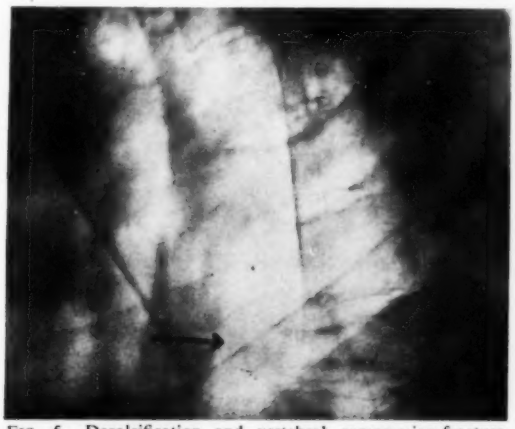

FIG. 5.—Decalcification and vertebral compression-fracture after treatment with corticotrophin, cortisone, and prednisone.

M. A. BIRNSTINGL: SURGICAL DIAGNOSIS OF "CHRONIC PANCREATITIS"

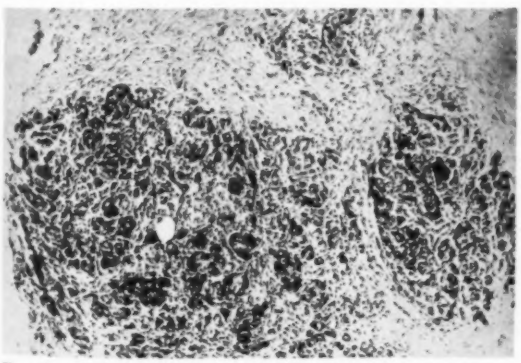

FIG. 1.—Pancreatic biopsy. Showing interlobular and interacinar fibrosis due to recent obstruction of pancreatic ducts. Male aged 67 with obstructive jaundice and mass in head of pancreas, diagnosed as "chronic pancreatitis." Death three years later from pancreatic carcinoma. (×64.)

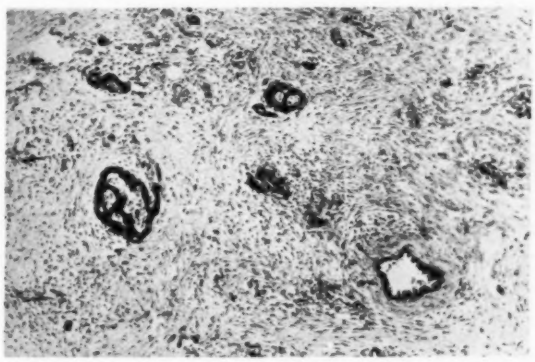

FIG. 2.—Pancreatic biopsy. Complete acinar replacement fibrosis, with scattered ductal remnants and islets of Langerhans, following ductal obstruction over many months. Male aged 64 with obstructive jaundice and mass in head of pancreas, diagnosed as "chronic pancreatitis." Death four months later from carcinomatosis. (×59.)

Figs. 3 and 4 overleaf

M. A. BIRNSTINGL: SURGICAL DIAGNOSIS OF "CHRONIC PANCREATITIS"

FIG. 3.—Extensive calcification in pancreas of woman aged 24 with chronic relapsing pancreatitis.

FIG. 4.—Barium-meal radiograph of male aged 31 with chronic relapsing pancreatitis, showing distortion of upper part of duodenum by pancreatic cyst and scattered pancreatic calcification.

NANCY K. CONN *ET AL.*: SYSTEMIC CANDIDIASIS DUE TO *C. TROPICALIS*

FIG. 1.—In right atrium vegetations extend from entrance of inferior vena cava (arrow bottom left), upwards around orifice of superior vena cava, and onwards to adjoining trabeculae (arrow top right).

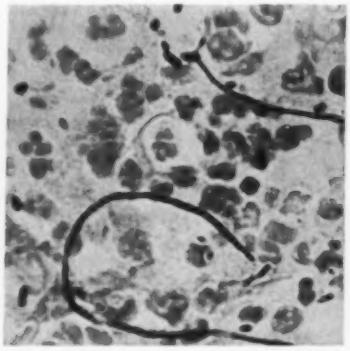

FIG. 2.—Direct smear from right atrial vegetation, showing *C. tropicalis* as mycelium and oval yeast-like cells. (Gram. ×618.)

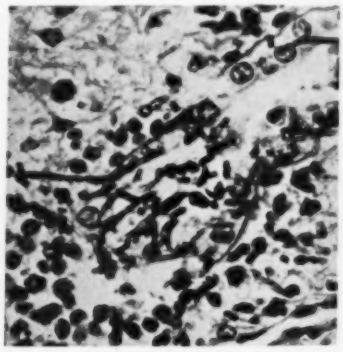

FIG. 3.—Renal collecting tubule containing *C. tropicalis* and surrounded by acute inflammatory exudate. (P.A.S. (McManus). ×500.)

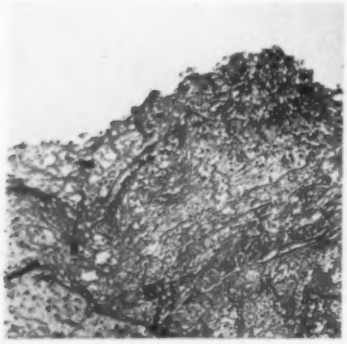

FIG. 4.—Portion of vegetation in right atrium showing colony of *C. tropicalis* surmounting laminated thrombus. (H. and E. ×100.)

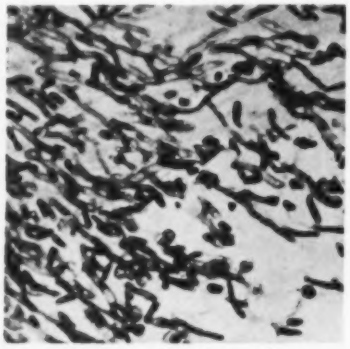

FIG. 5.—Portion of one of small vegetations on pulmonary artery consisting of *C. tropicalis* as mycelium and oval yeast-like cells. (P.A.S. (McManus). ×500.)

FIG. 6.—Glucose broth blood culture after 24 hours' incubation at 37° C., showing colonies of *C. tropicalis* deposited at base of bottle.

H. G. RICHMOND: SARCOMA INDUCTION BY IRON-DEXTRAN COMPLEX

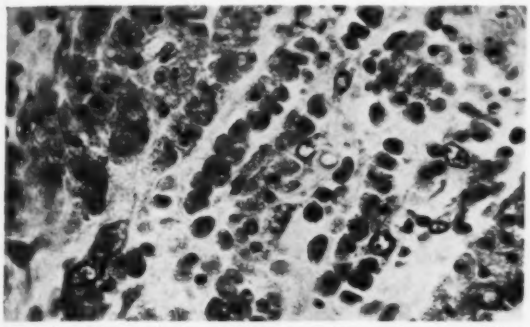

FIG. 1.—Biopsy of site of injection at 16 months. Iron-laden histiocytes mingled with aberrant cells. (H. and E. ×300.)

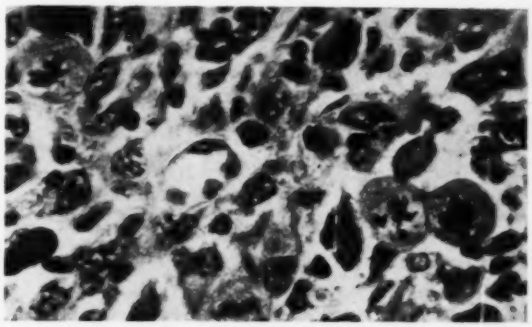

FIG. 2.—Biopsy from same rat as Fig. 1 five weeks later. Pleomorphic tumour showing numerous mitotic figures. (H. and E. ×450.)

B. S. KHAIRA, W. B. YOUNG, AND P. de V. HART: MELIOIDOSIS

FIG. 1

FIG. 1.—Case 1. Ill-defined patchy opacities in upper zones of both lungs, with larger homogeneous opacity in left mid-zone peripherally.

FIG. 2.—Case 1. Porosis of lower cervical and upper dorsal spine and upper ribs.

FIG. 2

FIG. 3.—Case 2. Infiltration in left upper and middle zones of left lung.

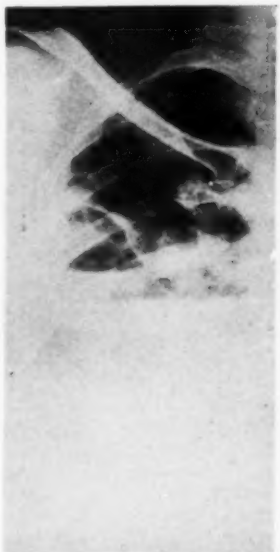

FIG. 4.—Case 3. Loculated hydropneumothorax on right side. Right upper lobe partially collapsed and containing medium-sized abscess cavity surrounded by irregular area of consolidation.

G. N. CHANDLER *ET AL.*: CHARCOT'S ARTHROPATHY AFTER HYDROCORTISONE

FIG. 1.—Radiograph of right hip in 1951. Note moderate osteoarthritic changes.

FIG. 2.—Radiograph of right hip after six months' treatment. Note marked osteoarthritic change with loss of joint space, sclerosis, and flattening of femoral head.

FIG. 3.—Radiograph of right hip after 18 months' treatment. Note gross destruction of femoral head and roof of acetabulum.

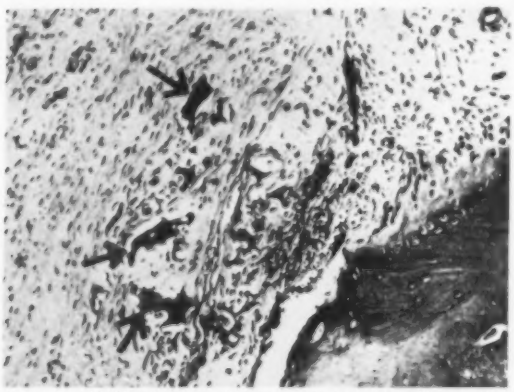

FIG. 4.—Field showing focus of bone resorption, with angulated fragments of necrotic bone indicated by arrows. There is some perivascular cellular reaction. (H. and E. ×80.)

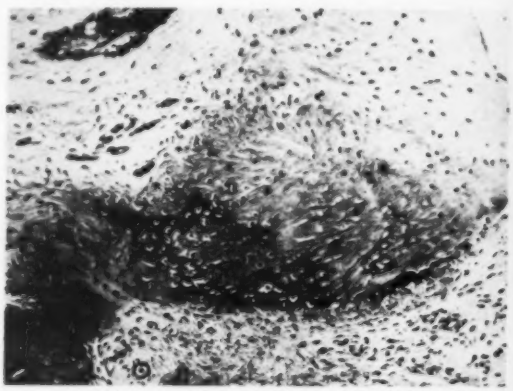

FIG. 5.—Field showing focus of new metaplastic bone formation spreading out from old bone seen (striated) in top left-hand corner. (H. and E. ×80.)

G. P. BAKER AND N. H. MARTIN: SYMPTOMLESS MYELOMATOSIS

FIG. 1.—Radiograph of lumbar spine, February 9, 1953.

FIG. 2.—Radiograph of lumbar spine, February 7, 1957.

FIG. 3.—Radiograph of lumbar spine, August 10, 1957.

case there was no radiological evidence of pancreatic disease. In all the cases in which barium-meal examination revealed abnormalities subsequent operation showed that the pancreas was enlarged. In the case with radiological changes in the mucosal pattern and duodenal irritability active subacute inflammation of the pancreas was found on exploration.

The biliary tract was not investigated radiologically in most of the cases in Group II, nor was recourse had to any operative radiographic procedures.

Operative Findings

One patient had had cholecystectomy 14 years previously, followed seven years later by operative removal of a residual calculus in the stump of the cystic duct. Another was found at operation to have some thickening of the wall of the gall-bladder, which contained no stones and which it was not thought necessary to remove. These two patients were the only ones with disease of the gall-bladder, and no biliary calculi were discovered in the remainder of the patients in this group.

The principal operative findings are shown above in Table I. Dilatation of the supraduodenal part of the common bile duct was recorded in three patients, all of whom had had clinical jaundice previously. In one of these the gall-bladder was also considerably distended, but the other presented the thickening already referred to.

None of the patients was explored during the initial attack of pancreatitis, since, as already stated, the earliest episodes were less severe than the later ones. There was no case of fulminant or severe acute pancreatitis, but three patients were explored during what might be termed subacute attacks. The pancreas was oedematous and enlarged, and there were oedema and fat necrosis in the surrounding tissues. Laparotomy in the remaining cases was undertaken in a quiescent phase of the disease. In four of these a diffuse enlargement, firmness, and irregularity of the pancreas was present; in a further case the head of the organ appeared to be most affected, being enlarged, hard, and nodular. There is no accurate record of the findings in the two remaining cases.

Pancreatic cysts were discovered at operation in two cases. In one of these cases a single cyst, 2½ in. (6.4 cm.) in diameter and containing a number of small chalky calculi, was present in the lower part of the pancreas head. In the second case there was clinical evidence of duodenal obstruction in addition to pain of characteristic pancreatic type. Operation revealed active inflammation of the pancreas, which presented a polycystic appearance, with distortion and compression of the duodenum. This interesting case has been reported previously (McGrigor, 1953).

In an attempt to relieve the symptoms of the 10 patients in this group 17 surgical operations were performed. In view of the small number of cases and the variety of procedures adopted, it would not, generally speaking, be profitable to describe either the methods used or the effects achieved. However, the results of internal biliary drainage are of some interest, since in the three cases in which this was carried out symptoms were completely relieved for at least seven years. At the end of this time one patient suffered a mild attack of pancreatitis; the operation in this case had been cholecystojejunostomy. Another patient had also had this procedure, and in the third case the operation was choledochoduodenostomy.

Pathological Findings

The macroscopical findings at operation have already been described. Only two patients with relapsing pancreatitis died. On one of these necropsy was performed at another hospital, and revealed the cause of death as rupture of a previously unsuspected aneurysm of the abdominal aorta; the appearance of the pancreas was unfortunately not recorded. The other patient died with a clinical picture strongly suggestive of cholangitis and biliary cirrhosis, nine years after the establishment of pancreatic disease at laparotomy.

Although, with two exceptions, accurate descriptions of the appearance and extent of involvement of the pancreas at operation are recorded, the histological material is scanty and pancreatic biopsy specimens were obtained in only four cases. These sections are either small fragments taken from the surface of the pancreas, or represent part of the wall of a cyst. Although showing dense collagenization and some chronic inflammatory-cell infiltration, little pancreatic tissue is recognizable in any of the sections. Those histological changes that can be distinguished are largely non-specific, and it has not been possible to draw conclusions from the results of re-examination of any of this material.

Discussion

The Diagnosis of "Chronic Pancreatitis"

Obstructive jaundice severe enough to require surgical relief is an uncommon complication of non-malignant pancreatic disease. Comfort *et al.* (1946) found only three patients with a history of clinically manifest jaundice in a series of 29 patients with chronic relapsing pancreatitis who showed no evidence of disease in the remainder of their biliary tracts. In all these patients the jaundice was of mild severity. Nevertheless, Fraser (1938), in a review of 1,035 patients with pancreatic disease undergoing surgical treatment for obstructive jaundice, was able to find 238 cases in which the operative diagnosis was "chronic pancreatitis." The immediate post-operative mortality in this series was 19.8%, a figure which seems remarkably high when the normal course of cases of chronic pancreatitis which do not require surgery is considered.

A possible explanation for the large number of patients with "chronic pancreatitis" requiring surgical treatment for jaundice in Fraser's series, and for the high subsequent mortality, would be that the diagnosis may in some cases have been incorrect. The present finding of 10 patients with obstructive jaundice in whom a diagnosis of "chronic pancreatitis" was made at operation and all of whom died from pancreatic carcinoma within the next three years lends support to this hypothesis, and suggests that the index of error in diagnosing "chronic pancreatitis" may well be higher than the figure of 16% put forward by Fraser. The clinical findings encountered in the patients of Group I of the present series were strongly suggestive of malignant disease. This likelihood was supported by the age of the patients and the short duration of their illness. The findings at operation provided further presumptive evidence of the presence of carcinoma, since they included the presence of a tumour in the pancreas in nine patients, seven of whom had

obstructive jaundice. Nevertheless, a histological report of "chronic pancreatitis" led to its acceptance as providing the most likely diagnosis of the true nature of the disease.

The interpretation of pancreatic biopsy material is notoriously difficult, the principal reason being that the pathologist is seldom offered more than a superficial fragment of the gland. Since in the early case of pancreatic carcinoma in which the operative diagnosis is doubtful the neoplasm most frequently lies deeply in the vicinity of the major ducts, it is unlikely that a specimen of neoplastic tissue will be obtained. However, it is frequently possible to identify the histological effects of ductal obstruction in such biopsy material, and a report of "chronic pancreatitis" upon such a picture will inevitably confuse the surgeon. This type of misinterpretation of surgical biopsy specimens occurred in eight of the 12 cases in Group I.

The sequence of changes in the pancreas following obstruction to the ducts has been studied extensively in animals (Arnozan and Vaillard, 1884; Senn, 1886); it shows no essential difference from human pathological appearances. The classical account by Lancereaux (1877) of pancreatic lesions accompanying diabetes includes a description of parenchymal atrophy associated with ductal obstruction by pancreatic stones. In 1884 Norman Moore described three fatal cases from St. Bartholomew's Hospital in which he had observed the ductal dilatation and "cirrhosis of the parenchyma" occurring as a result of calculi in the ducts. That malignant disease often causes a similar type of lesion was emphasized by Senn (1886), Mayo Robson (1900), and Opie (1910). Both the latter authorities introduced a note of confusion, however, by referring to the lesions as one variety of "chronic pancreatitis." More recently detailed accounts of the pathological features encountered in obstruction of the ducts by carcinoma have been published by Grauer (1939) and by Haunz and Baggenstoss (1950). The recognition of these changes in the pancreas is of primary importance to both surgeon and pathologist.

Complete obstruction to the main pancreatic duct when the accessory duct is similarly blocked or otherwise incapable of taking over its function causes progressive dilatation of the main duct. The secondary ducts are often affected to a lesser degree. The changes are accompanied by the gradual development of widespread replacement fibrosis of the pancreatic acini, so that the part of the pancreas above the obstruction undergoes progressive shrinkage. The firm, nodular, and shrunken condition thus produced has been referred to by Léger and Bréhant (1956) as *pancréatite d'amont*. The ductal dilatation may be of considerable extent and form an irregular, cyst-like structure, the true nature of which may not be recognized at operation, as occurred in two cases in the present series. Such "cysts" are filled with a glairy, clear, or milky fluid which appears to consist of the secretion of hyperplastic mucus-secreting glands in the walls of the obstructed ducts and resembles the secretion of "white bile" in complete biliary obstruction. It should, however, be added that, owing to the interaction of a number of factors, distension of the ducts of the pancreas is by no means an invariable accompaniment of the obstruction of this system.

The principal histological effects of ductal obstruction as seen in the parenchyma are acinar destruction and lobular replacement fibrosis. Variations in the histological picture appear to depend largely on the duration and completeness of the obstruction, so that a number of stages are seen in the biopsy material from the patients in Group I. The fibrosis which develops when the obstruction has been present for only a few weeks shows mainly an interlobular and interacinar distribution; many clumps of acini can still be distinguished (Special Plate, Fig. 1). The small ducts may show marked proliferative activity, but the islets of Langerhans are often difficult to distinguish. When the obstruction is more long-standing, acinar replacement becomes more complete and the collagenization progressively denser. The final picture produced by pancreatic ductal obstruction over the course of many months is one of scanty, irregular remnants of the minor ducts, strangled in a dense mass of fibrous tissue in which scattered islets of Langerhans can be clearly seen (Special Plate, Fig. 2). The variable extent to which infiltration with chronic inflammatory cells is seen histologically in the cases of Group I is apparently unrelated to the duration of the obstruction. Its distribution does not suggest that it is an effect of infection within the ducts, and it seems more likely that it is a non-specific effect. Similarly, the occasional development of lymphoid follicles is comparable to that sometimes seen in the scar tissue in the neighbourhood of a chronic peptic ulcer and in similar pathological conditions.

No evidence of an underlying inflammatory process has been found in a review of the morbid anatomical material from Group I. The marked structural changes encountered have all been explicable as results of the presence of neoplastic disease in neighbouring parts of the pancreas. It is probable that ductal obstruction plays a major part in the causation of such lesions. The term "chronic pancreatitis" fails to take into account the obstructive factor, and implies an inflammatory aetiology for which the present material gives no support. Furthermore, by obscuring the basic pathology in many of the cases to which the term is attached, its use may lull the surgeon into dangerous inactivity.

Chronic Relapsing Pancreatitis

The clinical course of the cases of chronic relapsing pancreatitis in the present series has been essentially similar to that recorded in previous accounts (Comfort *et al.*, 1946; Léger and Bréhant, 1956; Hunt, 1957). The average age of onset was 45 years, which is 15 years earlier than the average in Group I. Five of the 10 patients gave a history of transient obstructive jaundice, in three instances accompanied by a significant degree of dilatation of the biliary passages. However, in these cases the sign was clearly related to an inflammatory episode of the pancreatic disease, so that it was not difficult to differentiate the clinical picture from that accompanying malignant obstruction of the bile ducts. A history of gall-stones was present in only one case.

None of the patients under consideration gave a history of alcoholism. Recently Owens and Howard (1958) have reported 32 patients with chronic relapsing pancreatitis all of whom were chronic alcoholics, which is of interest because the association appears to be uncommon in Great Britain.

The diagnosis of chronic relapsing pancreatitis is often difficult, but much help may be given by skilled radiology. Pancreatic calcification was present in 40% of the patients with this disease in the present series, which accords with the 48% reported by Comfort *et al.*

in a series of 29 patients. More interest attaches to the demonstration of changes in the duodenal loop on barium-meal examination, since, although such appearances are well recognized in the presence of malignant disease of the pancreas, they have received scant mention in most articles on pancreatitis. In the present series radiological evidence of pancreatic enlargement was obtained in only one of the seven patients in Group I who were subjected to barium-meal examination. However, of six patients with chronic relapsing pancreatitis thus investigated, enlargement of the pancreas was demonstrated in five. Although not all the patients with this disease were examined, the proportion indicates that barium-meal examination is capable of a high degree of diagnostic accuracy in relapsing pancreatitis when carried out by a radiologist with a special interest in pancreatic disease. Either calcification or pancreatic enlargement was demonstrated in 70% of the patients with this condition.

The exacerbations characteristic of chronic relapsing pancreatitis are similar to isolated attacks of acute pancreatitis, and the disease usually appears to originate in a typical episode of the latter condition. However, the factors responsible for the initiation of the relapses remain obscure, although the prolonged relief of symptoms which followed biliary diversion in three patients in the present series supports the evidence (Smith, 1957) that reflux of bile into the pancreatic ducts may be an important cause. The macroscopical and histological changes seen in the morbid anatomical material from patients with relapsing pancreatitis (Group II) are consistent with their probable origin as a sequel to recurrent inflammatory incidents in the parenchyma, but the material is inadequate to allow further speculation. The final histological picture usually found in this disease represents a combination of the effects of acute parenchymal inflammation with those of ductal obstruction due to several causes. The evidence produced by Edmondson *et al.* (1950) now makes it clear that in a large proportion of cases the pancreatic calcification encountered in relapsing pancreatitis occurs within the ducts and not in the parenchyma. It is known that calculi of this type often arise during the course of the disease (Comfort *et al.*), to which they must be considered to be a sequel in these cases. Moreover, such stones must themselves cause secondary effects upon the parenchyma, and this has been confirmed by Edmondson *et al.*, who found that ductal dilatation and acinar replacement fibrosis were more marked in their cases of chronic relapsing pancreatitis when calculi were present. It therefore seems likely that when a histological picture of ductal obstruction is found in relapsing pancreatitis it represents an effect rather than a cause of the disease. In the present material the effects of pancreatic ductal obstruction are not seen, in contrast to their predominance in the specimens in which a diagnosis of "chronic pancreatitis" had previously been made. Nevertheless, direct pancreatographic procedures have not been considered justifiable in any of the patients with chronic relapsing pancreatitis here described, so that it has not been possible definitely to exclude an obstructive factor as playing some part in the aetiology of the condition.

Summary

Clinical and pathological findings are reviewed in a series of 22 patients in whom the presence of pancreatic disease has been confirmed at operation.

In 12 patients a diagnosis of "chronic pancreatitis" was made on the operative findings, supplemented in eight cases by surgical biopsy. All of these died from pancreatic carcinoma within three years. An important cause of error in the pathological diagnosis of these cases has been a failure to recognize the structural effects of pancreatic ductal obstruction. The term "chronic pancreatitis" is an inaccurate description of this type of pathological change.

In the remaining 10 patients a clinical picture of chronic relapsing pancreatitis was supported by the macroscopical findings at operation and by a period of post-operative survival varying between six and 40 years. Radiological changes in the configuration of the duodenal loop were demonstrated by barium-meal examination in five of these cases, and pancreatic calcification was present in four instances. The histological findings in chronic relapsing pancreatitis are discussed.

I wish to thank Professor Sir James Paterson Ross and Mr. G. W. Taylor for encouragement and helpful criticism, and Professor J. W. S. Blacklock and Dr. R. A. Kemp Harper for facilities in the Departments of Pathology and Radiology. I am also grateful to the consultant physicians and surgeons of St. Bartholomew's Hospital for allowing access to patients under their care. I am indebted to the Photographic Department and Mr. P. Crocker for the illustrations.

The review represents part of the work carried out during the tenure of a B.M.A. research scholarship.

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In the second edition of *A Practice of Thoracic Surgery* (pp. 605, illustrated, 100s., Edward Arnold and Co., London, 1958), Mr. A. L. d'Abreu has brought the material on this advancing subject up to date. In the last few years much progress has been made in thoracic surgery, particularly of the heart and great vessels, and in this edition, as in the first, the author presents his own opinions, experience, and practice. He deals, too, with the perplexing problems that have arisen over selection of patients for surgery in pulmonary tuberculosis, and with the challenge of the steady increase in lung cancer—a challenge which is being met better than many think. Newer views on the treatment of disorders of the oesophagus are given. Chapters are included on lung function by Professor K. W. Donald, on cardiac catheterization by Dr. P. H. Davison, and on angiocardiography by Dr. R. Astley, and these have been revised in this edition. The book is excellently illustrated.

SYSTEMIC CANDIDIASIS AND ENDOCARDITIS DUE TO C. TROPICALIS

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[WITH SPECIAL PLATE]

Mucocutaneous candidiasis is a well-recognized complication of severe debilitating illness, and has become more common since the widespread use of antibiotics. It may precede systemic candidiasis, which sometimes manifests itself as a septicaemic illness with endocarditis. The following case is reported to emphasize the gravity of this complication and to record an endocardial lesion of unusual nature.

Case Report

Clinical History

The patient was a woman of 61 who had suffered from dyspepsia for 20 years. Symptoms had been severe for the last 12 months, and on admission to hospital she was grossly undernourished, weighing only 91 lb. (41.277 kg.), and had marked epigastric tenderness. Chronic rheumatoid arthritis affected the fingers, wrists, elbows, shoulders, and knees. A barium-meal examination showed scarring of the duodenal cap and a large gastric ulcer. Urine analysis was normal. Erythrocyte sedimentation rate (E.S.R.) 50 mm. in the first hour (Westergren); erythrocytes 4,400.000 per c.mm.; haemoglobin 9.6 g. per 100 ml.; P.C.V. 31%; total and differential white counts normal; plasma albumin 2.3 g. and globulin 2.9 g. per 100 ml.; blood urea nitrogen 11 mg. per 100 ml.

A modified Schoemaker type Billroth I gastrectomy was performed on June 6, 1957, for a simple gastric ulcer. Fifteen days later she was discharged well, weighing 90 lb. (40.82 kg.) Within two days fever with rigors and vomiting developed, and she was readmitted on July 11. She weighed 85 lb. (38.56 kg.) and looked ill, but no new abnormality was found. Urine analysis on four occasions was normal. W.B.C. 4,600 per c.mm. (neutrophils 57.5%, lymphocytes 33%, monocytes 7.5%, eosinophils 2.0%); E.S.R. 20 mm. in one hour; haemoglobin 13 g. per 100 ml. Radiographs of chest and infradiaphragmatic areas were normal. The fever persisted until July 13 (see Chart). She left hospital against advice on July 15, but had to be readmitted on the 19th because the rigors and vomiting recurred. She looked ill, her temperature was 103° F. (39.4° C.), and her urine contained numerous pus cells. W.B.C. 12,000 per c.mm., E.S.R. 42 mm. in one hour, haemoglobin 15 g. per 100 ml., P.C.V. 48%; serum electrolytes normal; blood urea nitrogen 17 mg. per 100 ml. Rehydrating intravenous infusion was maintained for 72 hours, and 1 g. streptomycin and 1 mega unit of penicillin per day were administered for seven days. The fever resolved and her general condition improved. Vomiting persisted, however, for the following four weeks, and a laparotomy was performed on August 16. The stoma was found to be narrowed by a plaque of fibrous tissue projecting into the lumen, and the obstruction was successfully relieved. There was no evidence of intra-abdominal sepsis.

Throughout the time from her admission on July 19 until her death 57 days later pus cells were constantly found in the urine, and *Escherichia coli*, *Proteus vulgaris*, and *Pseudomonas pyocyanea* were cultured on five different occasions from catheter specimens (see Chart). During this time she received a total of 28 g. streptomycin, 28 mega units of penicillin, 24 g. sulphadimidine, and 8 g. terramycin, each drug being prescribed according to the sensitivities of the urinary organisms.

High fever and rigors recurred on August 26, and thereafter her condition deteriorated. By now arthralgia, inanition, and anorexia were severe, and her body weight had fallen to 78 lb. (35.38 kg.). Because the arthralgia was resistant to analgesics she was given 37.5 mg. cortisone daily (total 525 mg.) from August 31 until her death 14½ days later. Intravenous infusion was maintained through a polythene catheter introduced into the inferior vena cava. Each day at least 2 litres of 20% glucose, 80 ml. absolute alcohol, and various electrolytes were administered by this route.

In the last seven days of her life she developed uraemia manifested by deepening coma and twitchings, rising blood urea nitrogen (from 10 mg. to 150 mg. per 100 ml.), acidosis (carbon-dioxide-combining power 9 mEq per litre), and hyponatraemia (serum Na 113 mEq per litre).

Blood cultures on September 8, 10, and 14 yielded growths of *Candida tropicalis*. On September 12 a throat swab, a vulvar swab, and a urine specimen were taken, and on culture each yielded growths of *C. tropicalis*. There was no clinical evidence of mucocutaneous candidiasis at this or any other time. She died on September 15.

Necropsy Findings

Necropsy was performed four hours after death. The abdominal wounds were soundly healed. The legs were oedematous. There were no obvious candida lesions of the mucosa of the alimentary or respiratory tracts or of the vagina. The stomach was in satisfactory post-operative condition, and no inflammatory changes were obvious in its wall. There was, however, a small quantity of organizing fibrino-purulent exudate between the anterior wall of the stomach and the under surface of the left lobe of the liver. The kidneys were about twice their normal size, and numerous yellow abscesses, measuring about 1 mm. in diameter, were present on their subcapsular and cut surfaces. The cortex was swollen and pale, the medulla was streaked by the linear abscesses of acute pyelonephritis, and the mucosa of the calices and pelves was inflamed. The mucosa of the urinary bladder showed marked inflammatory oedema without membrane formation. The heart was dilated. The valve cusps were normal, but on the right atrial endocardium large, flat, yellow-grey vegetations which were firm and fairly smooth extended from the entrance of the inferior vena cava towards the superior vena cava and thence anteriorly on to the adjoining trabeculae (Special Plate, Fig. 1). On the subaortic endocardium of the left ventricle there were several small, flat, circular vegetations which appeared to cover minute myocardial abscesses. On the intima of the trunk of the pulmonary artery were several pale vegetations, measuring about 1 mm. in diameter, resembling colonies on a culture plate. The liver was swollen, soft, and congested. The lungs showed only basal congestion and slight oedema. The spleen weighed 300 g. and was congested. Direct smears from the kidneys, the right atrial vegetation (Special Plate, Fig. 2), and the exudate between the stomach and liver contained numerous candida-like organisms. The kidney smears also contained coccal and bacillary organisms. *C. tropicalis* was isolated from the peritoneal exudate and the kidney surface.

Microscopical Examination

In the stomach the anastomosis was soundly healed and there was no evidence of intramural candida infection. The kidneys showed severe acute pyelonephritis with a predominantly polymorphonuclear inflammatory exudate; numerous yeast-like organisms were present in the tubules and in the small abscesses (Special Plate, Fig. 3). In the

heart the vegetation on the right atrium consisted mainly of laminated thrombus. The atrial myocardium did not appear to be infected, and the reaction in the affected portion of endocardium was mild. Colonies of yeast-like organisms were present on the surface of the vegetation (Special Plate, Fig. 4). The vegetations in the pulmonary artery were composed almost entirely of surface colonies of similar organisms (Special Plate, Fig. 5). Sections of the ventricular myocardium contained a few widely separated minute polymorphonuclear abscesses. Other organs showed toxic and congestive changes without evidence of infection.

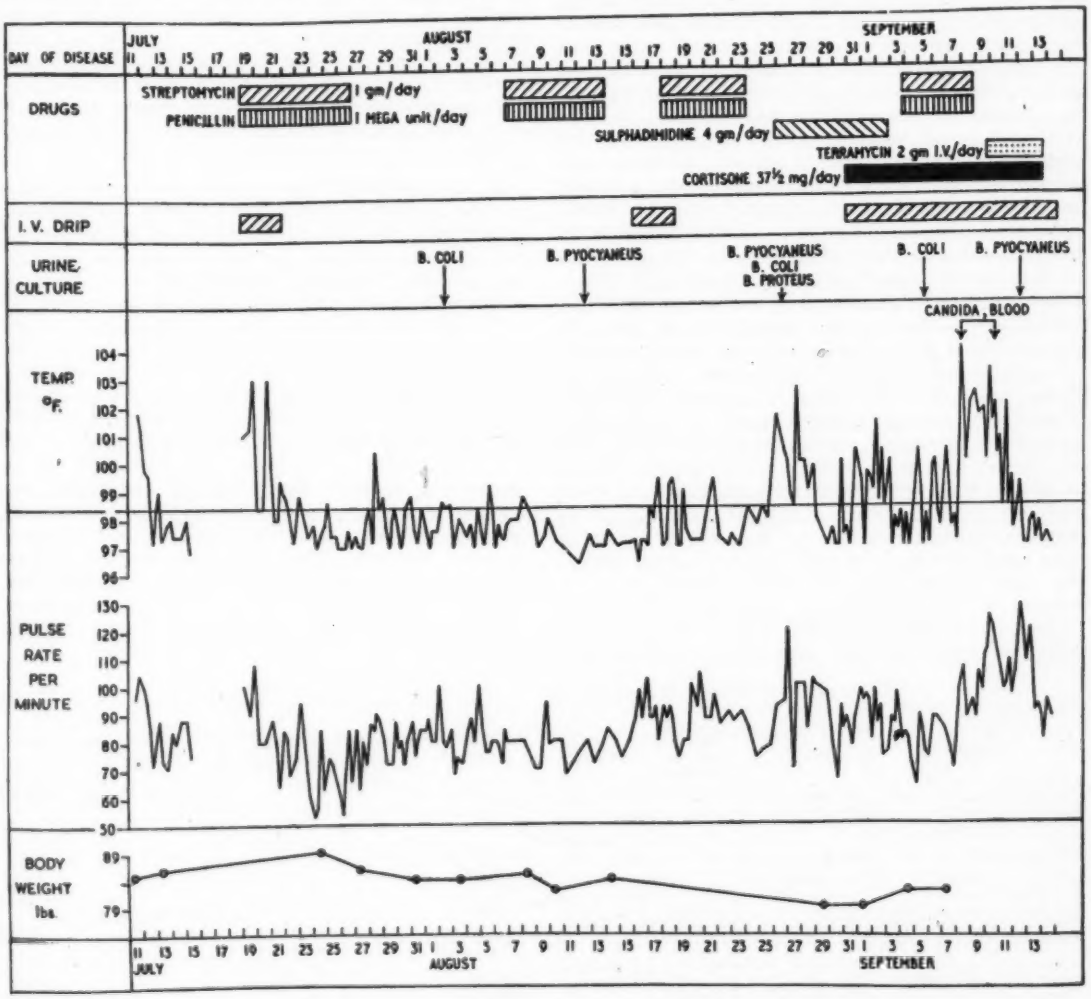
Identification of Candida

After 24 hours' incubation at 37° C. colonies were visible in all three blood-culture bottles, both on the surface and suspended throughout the broth; they were yellow, globular, and were ill-defined at their margins (Special Plate, Fig. 6). Stained films of these colonies revealed oval yeast-like cells. Sub-cultures on Sabouraud's glucose agar medium and corn-meal agar were incubated at 25° C. The inoculating wire was cut into the surface of the corn-meal agar medium. Specimens of urine and urethral discharge, and from the throat, and post-mortem specimens from kidney and peritoneum, were also inoculated on to similar media and incubated at 25° C. Within 24–48 hours colonies appeared on Sabouraud's medium which were smooth, matt, of creamy colour and granular consistency, and with a slight grittiness noted on manipulation with an inoculating wire, not found in typical colonies of *C. albicans*. The colonies had a distinct yeasty odour. Macroscopically, the colony on corn-meal agar appeared similar to that of *C. albicans*. Repeated microscopical examination revealed mycelium, pseudo-mycelium, blastospores, but no chlamydospores.

Biochemical tests gave the following reactions: glucose—acid and gas; lactose—nil; sucrose—acid and gas; maltose—acid and gas. The colony characteristics and biochemical reactions were identical in cultures from the blood, throat, urine, urethral discharge, and post-mortem specimens of kidney and peritoneum.

The identification of the *Candida* as *C. tropicalis* was confirmed by using the criteria laid down by Lodder and Kreger-Van Rij (1952), which included the use of malt extract, malt agar, and corn-meal agar media, also carbohydrate fermentation and carbohydrate and nitrate assimilation tests.

Mice of strains A., C.B.A., and University of Birmingham were inoculated with pure cultures (approximately 2,000,000 blastospores per 0.2 ml.). The cultures were pathogenic for all three strains, in particular strain A., in which bilateral renal involvement was severe.



GASTRECTOMY 6-6-57, DISCHARGED 21-6-57, 15TH POST-OPERATIVE DAY.

Chart showing course of illness, cultural findings, and treatment.

Discussion

Species of *Candida* can be isolated from the skin and mucous membranes of healthy individuals so frequently that it is often difficult to assess the significance of a single positive culture. For example, Dawkins *et al.* (1953) isolated such species as *C. albicans, C. krusei, C. parakrusei, C. tropicalis,* and *C. mycoderma* from the vagina in 57 of 500 healthy women. If, however, the fungus is isolated consistently, and from many different sites simultaneously, a diagnosis of candidiasis may be warranted.

Systemic candidiasis or moniliasis is a grave disease which may manifest itself as a generalized mucocutaneous eruption, as bronchopulmonary inflammation, or as a septicaemic illness. The kidneys, meninges, or bone may be isolated sites of deep candida infection, and the endocardium may also be involved. Monilial (candida) endocarditis was first reported in drug addicts habituated to self-administration of heroin or opium, but more recently it has been encountered in patients receiving antibiotic therapy (see Table). The valvular endocardium is principally attacked. Of 12 cases examined, post mortem vegetations were found on the mitral valve in six, on the aortic valve in three, and on both aortic and mitral valves in three; in eight cases the affected valves were thickened by fibrosis from previous disease. There were certain similarities between the disease in these patients and subacute bacterial endocarditis—the vegetations were usually large, and embolic phenomena such as systemic infarcts, focal embolic nephritis, and mycotic aneurysms were common. By analogy, therefore, the disease might be termed subacute monilial endocarditis. In this condition the less pathogenic members of the *Candida* species, such as *C. guilliermondi* and *C. parakrusei*, seem to be able to infect valves already damaged by disease (see Table).

The endocarditis in our patient differed from the reported cases of monilial endocarditis (1) in the species of infecting organism, (2) in the situation of the cardiac lesions, and (3) in the nature of the infective process. There have been no previous reports of endocarditis caused by *C. tropicalis*, although this organism has been isolated in a case of septicaemic candidiasis (Brown *et al.*, 1953), in osteomyelitis (Weingart *et al.*, 1942), and in broncho-pulmonary disease (Duroux *et al.*, 1954). The site of the endocarditis was also unique: the valves were unaffected, and the only large vegetations were in the right atrium where the blood entering from the inferior vena cava impinged upon the endocardium. Vegetations of the type present in the pulmonary artery have not been described previously; they probably resulted from surface infection by *C. tropicalis* carried in the stream of blood leaving the right ventricle. On the other hand, the small vegetations in the subaortic area of the left ventricle, although superficially similar, appear to have formed on the endocardium overlying small monilial abscesses in the myocardium. Lastly, the presence of abscesses in the myocardium and in the kidneys indicated that the infection was septicaemic. In this respect our case resembles Wolfe and Henderson's (1951) case and that of Kunstadter *et al.* (1952), and those cases, without endocarditis, in which *C. albicans* was the usual infecting organism (Duhig and Mead, 1951; Gausewitz *et al.*, 1951; Brown *et al.*, 1953; Schaberg *et al.*, 1955; Zimmerman, 1955; Matthias and Rees, 1956; and Barrett *et al.*, 1957).

It is not necessary to postulate that the severity of the renal lesions was conditioned by a previous bacterial infection, since monilial abscesses are most numerous in the kidneys in both experimental and clinical septicaemic candidiasis. *C. tropicalis*, however, was not isolated from the urine until a late stage of the illness, despite repeated cultures on a medium known to promote the growth of *Candida*. This suggests that, like the tubercle bacillus, the organism may escape less readily to the lower urinary tract than do coliform bacilli and other motile organisms. The urinary bacterial infection proved to be clinically misleading, since the continued pyrexia was attributed to bacterial pyelonephritis. It now seems probable that the cause of the pyrexia was, in fact, an unsuspected monilial infection.

In most recorded cases of subacute monilial endocarditis antibiotics either had not been administered, or had been given during an established infection which proved to be monilial. In contrast, antibiotic therapy has preceded monilial infection in most cases of septicaemic candidiasis, and, although severe candida infection is only likely to occur in debilitated subjects, there can be little doubt that prolonged administration of antibiotics increases the risk of this complication. Antibiotics have a similar action in rabbits infected by *C. albicans* var. *stellatoidea* (Foley and Winter, 1949), but they do not appear to potentiate growth *in vitro* of *Candida* (Woods *et al.*, 1951). They probably act by suppressing bacterial flora, reducing competition for nutritional factors, and thus indirectly enhancing monilial growth. Induced deficiency of vitamin-B complex has been advanced to explain their action (Harris, 1950), but Meenan (1957) concluded that vitamin-B administration did not influence the incidence of *C. albicans* infection in patients receiving antibiotic therapy.

Table Showing Details of Reported Cases of Candida (Monilial) Endocarditis

Authors	Patient's Age and Sex	Drug Addiction	Aetiological Importance of Antibiotics	Infecting Organism	Valves Affected	Valvular Fibrosis	Systemic Infarcts	Focal Embolic Nephritis	Probable Classification of Endocarditis
Joachim and Polayes (1940)	M 48	Heroin	Nil	C. parakrusei	Aortic		+		Subacute monilial endocarditis
Wikler *et al.* (1942)	M 49	,,	,,	,,	Mitral	+			,, ,, ,,
Helpern and Weiner		,,	,,	,,					
Peery		,,	,,	C. guilliermondi					
Luttgens (1949)	M 32	Opium	,,	No culture	Aortic and mitral				,, ,, ,,
Zimmerman (1950)	F 38	Heroin	,,	C. guilliermondi	Mitral	+	+		,, ,, ,,
Pasternack (1942)	M 45	No	,,	C. parakrusei	Aortic	+	+	+	,, ,, ,,
Wolfe and Henderson (1951)	F 57	,,	Doubtful	C. krusei	Mitral				Septicaemic endocarditis
Kunstadter *et al.* (1952)	M 7/12	,,	Unlikely	C. albicans	,,				,, ,,
Köhlmeier (1953)	M 41	,,	Doubtful	,,	Aortic and mitral	+		+	Subacute monilial endocarditis
Niel (1953)	F 60	,,	Nil	C. guilliermondi	,, ,,	+	+	+	,, ,, ,,
Koelle and Pastor (1956)	M 40	,,	Doubtful	C. albicans	Aortic	+			,, ,, ,,
Geiger *et al.* (1946)	F 19	,,	Probable	,,	Mitral	+	+		,, ,, ,,
Caplan (1955)	M 43	,,	,,	No culture	,,	+	+	+	,, ,, ,,
Present authors	F 61	,,	,,	C. tropicalis	R. atrial endocardium				Septicaemic endocarditis

In the present patient extreme debility and prolonged antibiotic therapy were probably the most important factors in the development of systemic candidiasis. Latterly the progress of the disease may have been accelerated by cortisone therapy and by intravenous administration of 20% glucose saline. Indeed, Duhig and Mead (1951) and Schaberg and his colleagues regarded the prolonged use of intravenous glucose saline as an important factor in establishing the infection in their cases. Some form of injection appears to be common to all cases of systemic candidiasis irrespective of the use of antibiotics. Here, however, infection from the alimentary tract may have occurred at operation, since local peritoneal exudate infected with *C. tropicalis* was present between the stomach and liver at necropsy. Systemic candidiasis has been reported after duodenal perforation or abdominal operations on a number of occasions (Brown *et al.*; Schaberg *et al.*; Caplan, 1955; Matthias and Rees; Barrett *et al.*).

This case illustrates the various clinical factors predisposing to the development of systemic candidiasis. The history suggests that *Candida* may proliferate in the blood of a patient without any clinical signs of systemic moniliasis appearing other than pyrexia. Unexplained pyrexia occurring in prolonged debilitating diseases, especially where antibiotics and intravenous alimentation have been used, is an indication for culturing the blood in media suitable for the growth of fungi.

Summary

A case of systemic candidiasis due to *C. tropicalis* infection is recorded, and the clinical features, bacteriological investigations, and pathological findings are described. *C. tropicalis* endocarditis affected the right atrium. Other cases of monilial endocarditis are reviewed, and the aetiology and pathogenesis of the condition are discussed.

We thank Dr. W. Sircus for permission to publish this case, and are indebted to Dr. W. Blyth and Mr. D. W. R. Mackenzie, of the Experimental Mycosis Unit, Department of Botany, Edinburgh University, for confirmation of the *Candida* species.

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INDUCTION OF SARCOMA IN THE RAT BY IRON-DEXTRAN COMPLEX

BY

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[WITH SPECIAL PLATE]

Pathological amounts of iron may accumulate in the body in a variety of conditions—for example, haemochromatosis and transfusional, malnutritional, and occupational siderosis. In all these conditions arguments for and against the cytotoxic effects of iron have been advanced, but the possibility that this metal plays any part in carcinogenesis has hardly been entertained. Therefore, in the belief that iron was non-carcinogenic if not altogether bland, an iron-dextran complex ("imferon," Benger Laboratories Ltd.) was deliberately chosen in order to establish a progressive mobilization or "hyperplasia" of histiocytes. This need arose when it had been discovered (Richmond, unpublished observation) that repeated subcutaneous injections of trypan blue commonly induced a pleomorphic histiocytic sarcoma in the rat at the site of injection. By a collateral series of experiments with a non-carcinogenic substance it was hoped to detect some critical difference between a "hyperplasia" and a neoplasia of histiocytes. This hope was not realized because another crop of pleomorphic histiocytic sarcomas histologically identical with those induced by trypan blue was obtained as detailed below.

All the rats belonged to a home-bred hooded strain in which no spontaneous tumours of this kind have previously been recognized in this laboratory. They were fed on Diet No. 1 (Thomson cube) supplemented with greens.

Experimental Procedures

Experiment 1.—The animals were all adult males within the weight range of 250–300 g. at the beginning of the experiment. (*a*) 40 received a weekly intramuscular injection of 0.4 ml. iron–dextran complex into the right upper thigh. Each dose contained 20 mg. of iron as ferric hydroxide in complex with low-molecular-weight dextran. (*b*) 12 received weekly intramuscular injections of 0.5 ml. "ferrivenin" (Benger) under ether anaesthesia, with occasional interruptions owing to the development of ulceration. Each dose contained 10 mg. of iron as saccharated oxide of iron. (*c*) 12 received weekly injections of 0.5 ml. low-molecular-weight dextran. (*d*) 12 received weekly injections of 0.5 ml. normal saline solution.

Experiment 2.—The animals were weanling rats of both sexes averaging 48 g. in weight. (*a*) 20 males and 20 females were given twice-weekly intramuscular injections of iron–dextran complex into the right upper thigh in graduated dosage according to weight—namely, 0.1 ml. up to 100 g., 0.2 ml. up to 150 g., 0.3 ml. up to 200 g., and 0.4 ml. thereafter. This regimen was stopped after three months, each animal

having received 9.5 ml. iron–dextran complex. (*b*) 6 males and 6 females received corresponding volumes of low-molecular-weight dextran solution.

Results

In Experiment 1, 17 of the 40 animals receiving iron-dextran complex were killed during the early months, but 16 of the remaining 23 developed tumours at the site of injection between the 11th and 16th months of the experiment. Rats given low-molecular-weight dextran and saline did not develop tumours, nor did those animals receiving saccharated oxide of iron over a period of 17 months. In the last group the injections commonly gave rise to necrosis which might be associated with ulceration of the overlying skin and secondary infection; collections of siderocytes and an abundant granulation-tissue reaction were demonstrated on histological examination, but no evidence of malignancy was seen.

In Experiment 2, tumours developed in 10 female and 12 male rats at the site of injection from six to eight months after cessation of iron treatment, while those receiving dextran alone showed no tumour formation.

Histological Observations.—The essential change at the site of injection of the iron–dextran complex in the early stages is a progressive accumulation of histiocytes laden with iron pigment. Previous to the inception of tumours it has been established from biopsy material that occasional histiocytes develop enlargement and hyperchromatism of the nucleus associated with mitotic activity and other aberrant changes (Special Plate, Fig. 1). Therefore it is deduced that the neoplastic process originates in such histiocytes, which gradually lose their avidity for iron as the neoplasia gathers momentum. The characteristics of established tumours vary from spindle-cell sarcoma to a highly pleomorphic growth including many giant cells and exhibiting numerous mitoses (Special Plate, Fig. 2). Iron-laden histiocytes are distributed throughout the tumour, and, while some neoplastic cells contain traces of the metal, the great majority are free from it.

Transplantation.—Metastases were not observed in the tumour-bearing animals, but transplantation of the tumour was successful in three of four examples in which this was attempted. In the first generation the transplants grew slowly after a lag period of four, six, and eight months respectively, but more rapidly in subsequent generations. One line is now in the 27th generation, requiring transplantation every four weeks. Histologically, some degree of the initial pleomorphism is still seen in this transplanted tumour, but the growth is essentially a spindle-cell sarcoma.

Discussion

From these observations it is clear that intramuscular injection of iron–dextran complex is carcinogenic in the rat. It is also clear that the dextran fraction alone is free from carcinogenic activity under the conditions of the experiments, so that iron is likely to be the responsible agent. The possibility that this effect is exerted only when it is in complex with dextran has been considered, but this is regarded as unlikely owing to the fact that the dextran is rapidly split off after injection and the iron chelated with protein to form haemosiderin (Golberg, 1957). The attempt to decide the issue by the repeated injection of saccharated iron was upset by the occurrence of necrosis and ulceration, necessitating interruptions in the sequence of the injections. These findings in the rat following the injection of iron–dextran complex have been confirmed in a small series of mice at the Chester Beatty Research Institute (Haddow, 1958).

The clinical significance of these observations cannot be assessed pending an elaborate study of the many factors involved. The iron–dextran complex has been widely used in the treatment of iron-deficiency anaemias in adults (Scott and Govan, 1954; Cappell *et al.*, 1954; Baird and Podmore, 1954; Jennison and Ellis, 1954; Scott, 1956) and in infants (Gaisford and Jennison, 1955). The amount administered in the adult human subject will vary according to the need of the patient, up to 54 ml. being recommended by the manufacturer for a patient weighing 180 lb. (81.64 kg.) with an observed haemoglobin value of 50%. Against this may be contrasted the volume administered to the rat—namely, 17.6–25.6 ml. in Experiment 1 (*a*) and 9.5 ml. in the younger rats of Experiment 2 (*a*). Therefore it will be evident that the dosage used in these experiments is relatively massive—some 200–300-fold—when compared with the therapeutic dose—for example, 20–40 ml. for a 70-kg. man.

Hitherto iron has not been proved to be a carcinogenic agent, and this finding may have some wider implications. For example, frequent reports appear in the literature concerning the high incidence of hepatoma supervening on the cirrhosis of the liver which is associated with haemochromatosis. The usual incidence of liver cancer in relation to cirrhosis of Laennec type has been placed at 3 to 7% (Anderson, 1957). In contrast, Warren and Drake (1951) reported the development of hepatoma in 18% of their cases of haemochromatosis, Stewart (1931) found an incidence of 10% in 151 collected necropsy cases of haemochromatosis, and Willis (1953) found three cases of hepatoma in seven necropsies on patients suffering from haemochromatosis. These figures suggest that there is a special tendency for the cirrhosis of haemochromatosis to undergo malignant change as compared with cirrhosis in general. While Edmondson and Steiner (1954) believed that the difference might be due to patients with haemochromatosis living longer than patients with portal cirrhosis of Laennec type, the present experiments suggest that gross iron deposition may well be the factor responsible. Incidentally, Branwood (1958) has investigated 100 examples of portal cirrhosis, of which slight to gross deposition of haemosiderin in the liver cells was observed in 33 cases. Hepatoma supervened in six of the 100 cases of portal cirrhosis, and all six were included in the group showing haemosiderosis.

The evidence submitted also suggests that iron may be the important causal agent in the development of pulmonary carcinoma in haematite miners. The rising incidence of pulmonary carcinoma in haematite miners was pointed out by Faulds and Stewart (1956), who found 17 cases of carcinoma of the lung in 180 necropsies (9.4%). These lungs contained silica as well as iron, but there was no similar incidence of pulmonary carcinoma in coal-miners dying of silicosis in the same area of West Cumberland, nor had this been reported from other coal-mining areas. Faulds added more information in 1957 with regard to the incidence of pulmonary carcinoma in haematite miners, making it clear that the only other silicious trades associated with

an increased incidence of carcinoma of the lung were asbestos workers, moulders and foundrymen, and chromate workers, and pointing out that asbestos and chromate contain varying amounts of iron in their chemical composition. In this context there is further support from the work of Campbell (1940, 1943), who exposed mice of a strain susceptible to lung cancer to an atmosphere laden with ferric oxide. He found that 32.7% of the mice exposed to the dust developed tumours of the lung compared with 9.6% of the controls, while mice exposed to a mixture of silica and ferric oxide showed a tumour incidence halfway between these figures (19.4%).

Mode of Action of Iron.—It has been observed that the histiocytes at the site of injection and elsewhere in the body (for example, Kupffer cells) contain, in addition to iron pigment, globules of a lipofuscin pigment of ceroid nature. The development of ceroid throughout the tissues of the body is one of the characteristics of vitamin-E deficiency (Mason, 1944), and in recent experiments Golberg and Smith (1958) have shown that the ceroid developing through iron overload can be largely prevented by supplementing the diet with α-tocopherol. It may therefore be inferred that one way in which iron influences intracellular metabolism is by blocking the antioxidant activity of vitamin E and possibly other antioxidants in the cell. The destruction or interference with these natural antioxidants allows oxidation of unsaturated fats to form the yellow pigment which is termed ceroid (Casselman, 1951). It remains to be shown whether this action of iron in the cell has any relation to the development of malignant change.

Summary

In the adult rat weekly-repeated intramuscular injections of iron–dextran complex induced sarcoma at the site of injection. A bi-weekly series of similar injections, begun in weanling rats and stopped after 12 weeks, also induced sarcoma at the site of injection some seven months later.

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MELIOIDOSIS

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[WITH SPECIAL PLATE]

Melioidosis is an uncommon yet highly lethal disease caused by *Pfeiferella whitmori*, which closely resembles the organism responsible for glanders in animals. The disease was first reported by Whitmore and Krishnaswami in 1912 from necropsies on vagrants in Rangoon. In 1932 Stanton and Fletcher, of the Institute for Medical Research, Kuala Lumpur, Malaya, collected 83 cases of human infection from the literature—six of them in Europeans, and only nine of which were diagnosed before death. In this series there were only two survivors. Couture in 1935 reported 35 cases with a 95% mortality, and since then single instances or small series of cases have been recorded by a number of authors.

In the past the disease has been restricted to that part of Asia east and south-east of India, but in recent years isolated cases have been reported in Great Britain, the U.S.A., and South Africa among nationals who have returned from periods of residence in these endemic regions.

We have recently seen three patients with this disease in Malaya. We report them because they demonstrate the successful outcome that may be expected in cases suitably treated, and also because, owing to the large numbers of men and women of various nationalities who visit Malaya, isolated cases may be expected almost anywhere in the world.

Case 1

A 50-year-old male Chinese vegetable seller was admitted to the General Hospital, Kuala Lumpur, on March 21, 1955, complaining of cough and fever of two weeks' duration. There was much purulent sputum, at times blood-stained, and he was wasted and looked toxic. Temperature 100.6° F. (38.1° C.), pulse 120, respirations 30. There were signs of consolidation in the right infraclavicular region, and a pleural rub in the left mid-axillary line associated with a few moist sounds. Liver and spleen were not enlarged, and no lymph nodes were palpable. Hb 7.7 g. per 100 ml.; W.B.C. 11,800 per c.mm.; E.S.R. 83 mm. in one hour (Westergren). Sputum examination repeatedly negative for acid-fast bacilli. Radiography showed ill-defined patchy opacities in the upper zones of both lungs, with a larger homogeneous opacity in the left mid-zone peripherally (Special Plate, Fig. 1). There was a large soft-tissue swelling in the root of the neck on the left side.

A provisional diagnosis of pulmonary tuberculosis was made, and streptomycin, 1 g. daily, and isoniazid, 100 mg. thrice daily, were administered. By the eleventh day the fever had subsided, but treatment was continued up to a total of 31 g. of streptomycin. Despite this an abscess developed in the right supraclavicular fossa from which dark, offensive material was aspirated. No organism was demonstrated on smear, but some haemolytic streptococci

were grown on culture. Shortly afterwards a cold abscess developed over the upper dorsal spine, and on June 15, 1955, some cheesy material containing pus cells and Gram-positive cocci was aspirated from it, but culture for tubercle bacilli proved negative. Radiography showed that the bone texture of the lower cervical and upper dorsal spine and the upper ribs was abnormally porotic (Special Plate, Fig. 2). A homogeneous opacity extended laterally over the apices of both lungs and appeared to be continuous with the soft-tissue swelling at the base of the neck; and on the left side the upper border of the second rib and the neck of the first rib were eroded. The possibility of infection with *Actinomyces* or some other unusual organism was suggested. The abscess was aspirated again and no fungi were found in the smears, but *Pf. whitmori* was grown on culture. It was found to be sensitive to chlortetracycline, oxytetracycline, chloramphenicol, and streptomycin.

From July 21 the patient was given chloramphenicol, 1 g. thrice daily, for 10 days; and then chlortetracycline, 500 mg. six-hourly, for seven days. There was a spectacular improvement in his condition, with steady return to normal weight and vigour. On July 26 the abscess was again aspirated and 1 g. of chloramphenicol injected into the cavity. The result was dramatic, and what had been a chronic abscess resolved completely within a few days. *X*-ray examination showed complete clearing of the pulmonary shadows, the texture of the bones affected had returned to normal, and new bone was visible under the anterior longitudinal ligament bridging the spaces between the bodies of C6 and C7. To date the patient remains fit and well.

Case 2

A 42-year-old Chinese labourer was admitted to a small district hospital in Malaya on March 1, 1956, complaining of cough, purulent expectoration, fever, and progressive loss of weight. He was extremely emaciated and had a fever of 101° F. (38.3° C.). Some scattered soft crepitations were audible in both lungs. Hb 7.4 g. per 100 ml.; E.S.R. 65 mm. in one hour (Westergren). Sputum examinations were negative for tubercle bacilli, and blood films for malarial parasites. *X*-ray examination of the chest was interpreted as showing tuberculous infiltration in the left upper and middle zones with cavitation, and treatment with streptomycin, 1 g. daily, with P.A.S. and isoniazid was started. After 30 g. of streptomycin his condition was so improved that treatment was stopped; but because of a slight return of fever a second course was given, which lasted until June 14. A radiological opinion by one of us at this time was that there was a chronic abscess in the upper lobe of the left lung—probably not tuberculous (Special Plate, Fig. 3).

On June 20 a small abscess appeared in the suprasternal notch which gradually increased in size, and this was aspirated. No acid-fast bacilli were found on smear, but culture yielded a growth of *Pf. whitmori*. Sulphadiazine (total dose 36 g.) and chlortetracycline (total 37.5 g.) were then administered, and the abscess healed. His general condition continued to improve.

On September 8, 1956, he was admitted to the General Hospital, Kuala Lumpur, again complaining of cough. Repeated examination and culture of sputum proved negative. Radiography showed an increase in lung markings with soft, coarse mottled opacities scattered throughout both lung fields. Chloramphenicol, 250 mg. four times a day, was administered for nine days, and a second course of seven days' duration was given a month later. The cough ceased, but the radiographic appearances have remained unchanged for several months, although the patient has apparently fully recovered.

Case 3

A 46-year-old Sikh watchman, who since 1948 had had insulin intermittently for diabetes, was admitted to the General Hospital, Kuala Lumpur, in November, 1955, with a history of fever and occasional rigors for three weeks and more recent development of a cough and thick, purulent sputum. He was very ill and emaciated and looked toxic. He had a hectic fever, and bronchial breathing was audible in the right mammary region. W.B.C. 9,000 per c.mm. (polymorphs 71%, lymphocytes 29%); Hb 12.6 g. per 100 ml. No acid-fast bacilli were found in the sputum in spite of repeated searches.

Radiography of the chest (Special Plate, Fig. 4) revealed a loculated hydropneumothorax on the right side. The right upper lobe was partially collapsed and contained a medium-sized abscess cavity surrounded by an irregular area of consolidation. Examination and culture of aspirated fluid revealed no organisms. Twelve days' treatment with 1.2 mega units of penicillin daily brought no improvement. Oxytetracycline, 2 g. daily, was then given. The response was dramatic, with an immediate fall of temperature and drying up of sputum, though a low night fever (99° F. —37.2° C.) continued. Weight increased, but further *x*-ray films of the chest showed little alteration.

A month after admission the pleural fluid had changed to thin, greenish pus and a broncho-pleural fistula developed. *Pf. whitmori*, sensitive to chloramphenicol and the tetracyclines, was isolated by culture. He was given 2 g. of chloramphenicol and 3 g. of chlortetracycline daily by mouth; and each day the empyema pockets were aspirated and 100 mg. of tetracycline solution and 500 mg. of chloramphenicol powder in suspension instilled. By the end of a week the lung had expanded well, and after another week the abscess in the right upper lobe was no longer visible on the radiographs. The patient was discharged two weeks later free of symptoms, having gained 30 lb. (13.6 kg.) in weight. A year later he was fit and well.

Discussion

Aetiology.—The causative organism of melioidosis was first identified by Whitmore in 1913. But there is no general agreement on its classification, and it has been variously named *Pfeiferella whitmori, Pf. pseudomallei, Bacillus whitmori, Flavobacterium pseudomallei, Actinobacillus pseudomallei,* and *Loefflerella whitmori.* Morphologically it is very closely related to *Pf. mallei,* the organism responsible for glanders, from which it can be differentiated only on culture.

The mode or source of infection is unknown. At first Whitmore and Krishnaswami thought that the disease was the result of syringe inoculation, as many of their patients were morphine addicts, and they called it "morphine injector's septicaemia." Later Whitmore suggested that food contaminated with the excreta of infected rodents, probably rats, was the commonest source; and this theory has been accepted by several later observers in spite of the observations of Stanton and Fletcher (1932) and Alain *et al.* (1949) that it is rare to find rats infected with the disease in large surveys carried out to detect plague. Blanc and Baltazard (1941) showed that both the rat flea, *Xenopsylla cheopis,* and the mosquito, *Aëdes aegypti,* can harbour and transmit the organism, so that the possibility of an insect vector exists, especially as the disease has been known to occur in guinea-pigs, monkeys, rats, rabbits, dogs, and cats. Two fatal cases in horses have occurred in Malaya, and infected goats have been found in Malaya and Australia.

The apparent immunity of laboratory technicians working with *Pf. whitmori* cultures, and of attendants handling infected laboratory animals, suggests that man is not readily susceptible. Hennessy (cited Stanton and Fletcher, 1932) records a case in which the infection

occurred at the site of a dog-bite; but direct man-to-man infection has never been reported, though cases with severe pulmonary changes and discharging abscesses have been nursed in general wards.

Pathology.—At necropsy lesions are frequently demonstrated in lungs or bowel, and it seems likely that infection is by ingestion or by inhalation of the organism. In all of our cases there were manifest pulmonary lesions, and we believe that these represented the original location of the disease.

The organism stimulates an acute inflammatory reaction and small abscesses are rapidly formed. These tend to coalesce and to increase in size, and, if superficial, to break down and discharge. Spread occurs directly along deep tissue planes, and dissemination by the blood stream is common, leading to numerous pyaemic abscesses, especially in the lung, liver, spleen, and kidney, and usually to the early death of the patient. Enlargement of draining lymph nodes does not seem to be a feature of the disease, though abscesses in the neck —often the lower cervical region—are not uncommon. When bone is involved it undergoes necrosis. Sometimes only the skin may be affected, as described by de Moor *et al.* (1932) and Sudibyo (1938), and presents as a nodular skin eruption or indolent ulcers with raised nodular edges.

Clinical Course.—The disease may present in many different ways; occasionally in a fulminating form, as a septicaemia, cholera, or severe bronchopneumonia, with extreme prostration and death within a few days. More commonly it runs a slower, but, in the absence of treatment, equally relentless and fatal, course of a few weeks or months. Gastro-intestinal symptoms may suggest dysentery or typhoid; or pulmonary manifestations may be those of a lobar pneumonia or lung abscess, or may resemble miliary tuberculosis. A severe pyelitis or cystitis may accompany other lesions, or be the presenting form of the disease. A pustular form has been described which bears a superficial resemblance to smallpox.

At the other end of the scale is the rare, apparently benign, form with no constitutional disturbances, the patient presenting with superficial abscesses from which the organism is obtained. One of us has recently seen such a case in a Malay rice farmer who presented with a large abscess on his forearm from which *Pf. whitmori* was isolated. With treatment, which consisted in giving chloramphenicol by mouth and aspirating the abscess, his recovery was rapid.

Occasionally cases survive the acute stage of the disease and progress to a subacute or chronic stage which lasts anything from several months to several years; and some cases present as a subacute or chronic progressive illness from the start. It is of interest to note that of the cases so far reported in the white races almost all have been of this type. There is no constant pattern of this form of the disease other than a subacute pyaemia, with the development of chronic abscesses in almost any part of the body, which may lead to persistent discharging sinuses. Pulmonary involvement is common, either in the form of an irregular nodular infiltration which progresses to a spreading suppurative pneumonia, or as a chronic empyema. The disease may present as a liver abscess which is usually at first mistaken for amoebiasis. Bone involvement is not uncommon.

Diagnosis.—Final diagnosis depends on isolation of the causative organism. Its recovery has been reported from pus, blood, urine, cerebrospinal fluid (Martin, cited Stanton and Fletcher, 1932), and sputum. Usually a direct smear or *in vitro* culture is positive, though it may be necessary to examine a number of different specimens. Occasionally the diagnosis is made only after guinea-pig inoculation. In spite of the fact that all three of our cases had manifestations of pulmonary disease, in none was the organism isolated from the sputum.

Serological tests are not of much help in the diagnosis of the more acute forms of the disease, because the patient usually dies before the antibody titre is appreciably raised. Indeed, it is doubtful if agglutination tests are of any value even in more chronic forms, for titres ranging from 1:10 to 1:600 have been found in apparently healthy individuals in Malaya, and cases with active melioidosis may give titres of no more than 1:40.

Olds and Lewis (1954) claim that a filtered concentrated extract of a broth culture of *Pf. whitmori* (melioidin) causes typical positive skin reactions when injected into goats suffering from active disease. So far this method has not been tried in man. Gutner and Fisher (1948) reported a persistently positive Paul–Bunnell reaction in high dilution in their case, and they suggest that melioidosis may be another source of false positive heterophile antibody reactions.

Radiology.—In all our cases the possibility of an unusual disease was suggested, and this led to a search for one of the rarer organisms and the successful isolation of *Pf. whitmori.*

Treatment.—Grant and Barwell (1943) were the first to report the beneficial effect of sulphonamides. Of these, sulphathiazole and sulphadiazine are probably the most effective. The organisms are also sensitive to certain antibiotics, though different strains vary considerably in this respect. The most generally effective antibiotics seem to be chlortetracycline and chloramphenicol. In seriously ill patients it is advisable to use a combination of antibiotics and sulphonamides, but sensitivity tests must be carried out in each case.

Conclusion.—The possibility of melioidosis should be kept in mind in any unexplained suppurative pulmonary disease in a patient living in, or recently returned from, south-east Asia. The organism should be particularly looked for if there are multiple abscesses, discharging sinuses, or evidence of bone involvement.

Summary

Melioidosis is an uncommon, but extremely serious, disease in man. Hitherto it has been almost entirely restricted to the inhabitants of south-east Asia, but in recent years cases have been reported in Great Britain, America, and south-east Africa among nationals who have returned from the Far East.

Three cases recently seen in Malaya are described because they illustrate the success of appropriate treatment in a condition which is almost invariably fatal if unrecognized.

The aetiology, pathology, clinical features, and treatment are briefly discussed.

We wish to thank the Director of Medical Services, Federation of Malaya, for permission to publish this paper, and to express our appreciation to Dr. John Whelan, senior

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CHARCOT'S ARTHROPATHY FOLLOWING INTRA-ARTICULAR HYDROCORTISONE

BY

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[WITH SPECIAL PLATE]

In 1868 Charcot described a group of cases of arthritis associated with locomotor ataxy and hemiplegia, and stressed the absence of the cardinal signs of inflammation in the involved joints. He attributed the absence of pain to joint anaesthesia ("L'absence de douleur dans ces cas pourrait dépendre de l'anesthésie articulaire"). Eloesser (1917) reproduced the pathological features of this condition by repeated joint trauma in cats whose limbs had been rendered anaesthetic by severance of the posterior nerve roots. This work was thought to confirm the theory of pathogenesis which attributes these neuropathies to the effect of single or repeated injuries to a joint which has lost its sensibility to pain. Soto-Hall and Haldeman (1940) studied 40 patients with neuropathic joint disease. These authors showed that the essential features, in order of development, were the appearance of joint effusion, followed by ligamentous relaxation leading to instability and deformity with thinning of the articular cartilage. Marginal fractures, subchondral bony sclerosis, patchy atrophy, loose-body formation, and new bone production completed the picture of severe destructive arthritis.

The use of hydrocortisone acetate by intra-articular injection in the local treatment of arthritis has become widely accepted since its introduction in 1951 by Hollander and others. Most reports stress the subjective benefit derived by patients. Side-reactions are few, and are limited to temporary local exacerbation of disease, occasional appearance of sensitivity, the introduction of sepsis, and the development of thrombophlebitis in the injected leg. Hollander (1953) reported an incidence of only 2.3% of adverse reactions after 8,696 hydrocortisone injections. Kendall (1958) had an even lower incidence (1.1%) of untoward effects in a series of 6,700 injections. There has been no suggestion that repeated intra-articular injections of hydrocortisone might seriously aggravate arthritis, yet such aggravation might be expected as a result of the relief of pain experienced from such treatment. Interference with the normal protective processes might well encourage undue weight-bearing and mobility, thereby accelerating the progress of joint destruction. This has, in fact, been our experience in 10 of 18 patients with rheumatoid arthritis given prolonged treatment during a controlled trial of intra-articular steroid therapy (Chandler and Wright, 1958).

The following report describes the rapid deterioration of an osteoarthritic hip following repeated hydrocortisone injections.

Case Report

A doctor's wife aged 66 was first seen in the Rheumatism Clinic of the General Infirmary at Leeds in May, 1956. She had had pain in the right hip with difficulty in walking since 1937. Apart from a course of physiotherapy given with temporary benefit in 1951, she had received no treatment. Radiography of the right hip at this time showed slight osteoarthritic change (Special Plate, Fig. 1).

Examination disclosed a thin, intelligent woman in obvious pain. Chest, heart, and abdomen were normal, and there was no neurological defect. The only abnormality was painful restriction of movement at the right hip-joint. There was no shortening of the limb. A radiograph of the right hip disclosed some progression of disease as compared with the earlier film. The differential agglutination test was negative and the erythrocyte sedimentation rate (E.S.R.) normal.

Treatment was begun with phenylbutazone, 200 mg. twice daily, and 50 mg. (2 ml.) of hydrocortisone acetate injected into the right hip-joint at approximately monthly intervals. After each injection she experienced great relief from pain, which lasted some three weeks on each occasion. Fig. 2 on the Special Plate shows the radiographic appearance six months after treatment was started. Injections were continued for a further 12 months, when 900 mg. (36 ml.) of hydrocortisone had been given. Re-examination then showed an extremely mobile, painless joint. There was 2 in. (5 cm.) of true shortening of the right leg. The rest of the clinical examination was negative. A radiograph of the right hip showed gross destruction of the femoral head and the roof of the acetabulum (Special Plate, Fig. 3). Blood Wassermann reaction was negative and E.S.R. normal.

Biopsy of the right hip (Mr. A. B. Pain) showed no unusual features in the portions of tendon and joint capsule examined (Dr. D. Harriman) beyond some non-specific connective-tissue proliferation and occasional small foci of foreign-body reaction. Muscular atrophy was advanced. Biopsy of bone examined by Professor C. E. Lumsden showed features of resorption (Special Plate, Fig. 4) and new bone formation (Special Plate, Fig. 5). One section of biopsy was sent to Professor D. H. Collins, who reported: "There are really no diagnostic features in this biopsy. Most of the bone in the section is of compact or cortical pattern and appears normal, but at its junction with the periosteal tissues there are certain progressive changes of resorption and regeneration such as one may encounter in any slow remodelling process. Rather large, thin-walled vascular spaces and some islets of new metaplastic bone are seen in part of the outlying connective tissues. There is no evidence of tuberculosis or other infection. The changes that we see may be encountered around an osteoarthritic joint or, indeed, a Charcot's joint, but there is nothing to

say which. The inflammatory reaction in the tissues is of a very low order such as may accompany any reconstruction of bone."

Culture from the right hip and guinea-pig inoculation showed no evidence of tuberculosis.

Discussion

This patient has been the subject of wide interest, and a number of opinions have been obtained in respect of the aetiology of her arthritis. All observers agree that osteoarthritis was the primary joint disease. The slow progression from onset in 1937 to the inception of treatment in 1956 contrasted with the florid advance of joint destruction culminating in complete disorganization during the period of therapy with intra-articular injections of hydrocortisone acetate. The final picture, both clinical and radiographic, was indistinguishable from the condition described by Charcot. There was no evidence of neurological disease. Rheumatoid arthritis, tuberculosis, and other infective processes were excluded by serological tests and the results of biopsy.

The striking similarity of this picture to that of neuropathic arthritis suggests that temporary suppression of pain of local origin by frequent intra-articular injection encourages a damaging degree of movement and weight-bearing. This in turn permits the development and rapid progression of joint destruction. The deterioration observed in this patient during treatment with locally injected hydrocortisone suggests that the procedure is potentially dangerous. This is particularly so since it has been our experience that symptomatic benefit from injections may lead to a vicious circle of dependence despite worsening disease. Careful radiological supervision is desirable if prolonged treatment by intra-articular injections of hydrocortisone and related compounds is undertaken.

Summary

The development of a severe destructive and relatively painless arthritis (Charcot joint) is reported during prolonged treatment of an osteoarthritic hip with intra-articular injections of hydrocortisone acetate. The need for careful radiological supervision during such treatment is emphasized.

We are indebted to Professor C. E. Lumsden for his helpful criticism.

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Remotivating the Mental Patient, by Otto von Mering and Stanley H. King (Russell Sage Foundation, New York, 1957; 216 pp., $3), is based on a survey of in-patient care in 30 mental institutions in the United States. In spite of crowded conditions and shortage of staff it was found that courageous and promising programmes of rehabilitation had been developed in some places. The authors consider that such experiments as the elimination of restraint, the encouragement of the patient's interest in his personal appearance, transformation of his environment into a more normal atmosphere, and the promotion of social and recreational activities, among other things, are justified by the results they produce. Guidance is given in carrying out these and other measures of rehabilitation.

SYMPTOMLESS MYELOMATOSIS

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[WITH SPECIAL PLATE]

Myeloma commonly presents with pain in the bones. Out of 97 patients with myeloma examined by Snapper *et al.* (1953), 92 suffered from bone pain. Other common presenting features are pathological fractures, vertebral collapse with associated neurological complications, renal impairment, anaemia, and recurrent pulmonary infections.

The patient whose history is here recorded has been under continuous observation for 5½ years. For four years she was free from any symptoms or signs, except that she had a persistently raised erythrocyte sedimentation rate (120–130 mm. in one hour by the Westergren technique), a moderate orthochromic anaemia (Hb 10.7 g. per 100 ml.), and a very high serum globulin (7–8 g. per 100 ml.). Sternal puncture showed some increase in plasma cells, but no abnormal forms.

Case History

The patient, a housewife aged 43, had been in good health until April, 1952, when she developed a small right pleural effusion following an attack of "bronchitis," and in May she was admitted to the Pleural Effusion Unit of Queen Mary's Hospital, Sidcup. The effusion resolved spontaneously, and she was discharged in August, 1952, when her chest was radiologically normal apart from pleural thickening. It was assumed that she had a primary tuberculous effusion, although no tubercle bacilli were isolated, but the Mantoux reaction was positive. The only unusual feature was that her erythrocyte sedimentation rate (E.S.R.) was persistently raised and remained in the range 117–131 mm. in one hour (Westergren). Estimation of her serum proteins showed a total protein value of 11.2 g. per 100 ml. (albumin 3.65 g., globulin 7.55 g.). The urine was normal and contained no Bence Jones protein.

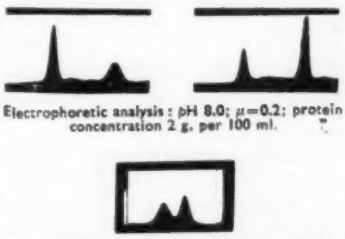
Electrophoretic analysis: pH 8.0; μ=0.2; protein concentration 2 g. per 100 ml.
Ultracentrifugal analysis: protein concentration 1 g. per 100 ml.

FIG. A.—Electrophoretic and ultracentrifugal analysis, December 14, 1952.

On return home she attended the Croydon Chest Clinic for surveillance, and at the end of December, 1952, she came under our observation on account of her very high E.S.R. She stated that she felt well and had no complaints. She looked fit and no abnormal signs were found, apart from slight pallor. Blood count was normal except for a mild orthochromic anaemia (Hb 10.7 g. per 100 ml.). E.S.R. 125 mm. in one hour. Sternal marrow from a puncture in February, 1953, appeared to be normal, but a differential

TABLE I.—*Serum and Urinary Proteins*

Date	Serum Proteins					Components Derived from Ultracentrifugal Analysis			Urinary Proteins	
	Total (g./100 ml.)	Components Derived from Electrophoretic Analysis							Bence Jones Protein	Total (mg./100 ml.)
		Albumin (g./100 ml.)	Globulins (g./100 ml.)			S_{20w}4·0	S_{20w}6·5	S_{20w}17–19		
			α	β	γ					
Aug. 52 ..	11·2	3·65		7·55*					Nil	Nil
Dec. 52 ..	10·9	3·45	0·6	0·85	6·0				,,	,,
Feb. 53 ..									,,	20
May 53 ..	11·0	3·4	0·7	0·9	6·0	40%	60%	Nil	,,	Nil
Feb. 54 ..									,,	50
Aug. 54 ..	11·6	3·8	0·7	0·8	6·3				,,	Nil
,, 56 ..	12·0	3·1	0·6	0·8	7·5				,,	50
Feb. 57 ..	13·8	3·9	0·6	0·9	7·9	35%	65%	,,	+	200
Oct. 57 ..	13·0	3·9	0·4	1·2	7·4				+	1,600
Dec. 57 ..	11·9	3·1	0·3	1·2	7·3	33%	67%	,,	+	800

* Total globulin by salt fractionation.

count showed 13% of plasma cells but no abnormal or immature forms. Radiography of chest, ribs, skull, spine (Special Plate, Fig. 1), pelvis, femora, and humeri revealed no abnormality. The urine was normal and contained no Bence Jones protein. The serum protein level was unchanged, total protein being 10.9 g. per 100 ml., and electrophoresis showed a marked increase in gamma-globulin (Fig. A). She continued to attend the out-patients' clinic at about three-monthly intervals, and she stated that she felt well and was free from symptoms up to and including her attendance in August, 1956—that is, four years since it was first known that she had a greatly raised E.S.R. and highly abnormal serum proteins. Physical findings were still normal, apart from pallor, but a trace of albumin in the urine (but no Bence Jones protein) was recorded for the first time. Her weight had very slowly fallen from 157 lb. (71.215 kg.) in 1952 to 131 lb. (59.420 kg.) in 1956. She insisted, however, that her usual weight was only about 135 lb. (61.235 kg.). The anaemia persisted (Hb 9.8 g. per 100 ml.) and the E.S.R. remained unchanged. Radiographs of skull and spine were normal.

In January, 1957, she complained of attacks of pain in the lumbar spine and also of febrile episodes which lasted for a week or so and made her feel very ill, but which were followed by recovery. In February, 1957, she was admitted to Mayday Hospital because of one of these attacks, and she was found to have tenderness over the sacrum and lower spine. Radiography showed osteoporosis and slight collapse of the bodies of several lumbar vertebrae, and there were some rather doubtful areas of erosion in the skull, humeri, and one rib (Special Plate, Fig. 2). Considerable albuminuria (200 mg. per 100 ml.) and Bence Jones proteinuria were found for the first time. Sternal marrow contained very numerous plasma cells. The diagnosis of clinical myelomatosis was thus confirmed. She made a satisfactory symptomatic recovery, and was discharged, at her own request, after three weeks. At home her pains returned, and she was readmitted with severe back pain in August, 1957. Radiographs now showed marked increase in the osteoporosis of the lumbar spine, with increasing collapse of all lumbar vertebrae (Special Plate, Fig. 3). She was treated with capsules each containing 0.5 g. of urethane and 25 mg. of "R 151" (Innes and Rider, 1955). This latter drug is an oral nitrogen mustard, β-naphthyl-di-(2-chloropropyl) amine. Dosage began with one capsule twice daily, and was increased four weeks later to one capsule three times a day. Leucopenia occurred at the end of seven weeks, and the dose was reduced to one capsule twice daily. After nine weeks the total leucocyte count fell to 900 per c.mm. and treatment was stopped. A week later the leucocyte count fell to 150 per c.mm., and

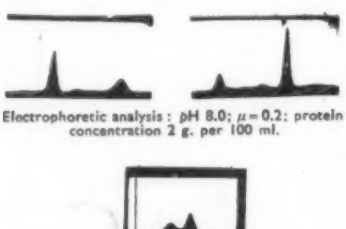
Electrophoretic analysis: pH 8.0; μ = 0.2; protein concentration 2 g. per 100 ml.
Ultracentrifugal analysis: protein concentration 1 g. per 100 ml.

FIG. B.—Electrophoretic and ultracentrifugal analysis, December 17, 1957.

TABLE II.—*Principal Haematological Findings*

Date	Haemoglobin (g./100 ml.)	Red Cells (per c.mm.)	White Cells (per c.mm.)	E.S.R. (Westergren: mm./hour)
Aug. 52 ..	10·4		5,400	131
Dec. 52 ..				128
Feb. 53 ..	10·7	3·5	5,050	131
June 53 ..	11·0	3·3	4,200	125
Nov. 53 ..				120
Feb. 54 ..	12·0	3·7	8,700	131
Mar. 55 ..	8·9	2·9	4,400	137
May 55 ..				147
Aug. 56 ..	9·8	2·8	3,400	141
Jan. 57 ..	8·6	2·8	4,800	146
June 57 ..	8·9			144
July 57 ..	8·3		5,000	153
Aug. 57 ..	8·6		2,800	
Sept. 57 ..	7·4*		150	
			850	
Oct. 57 ..	(1) 5·6†		2,500	
	(2) 9·0		1,700	153
Dec. 57 ..	10·4	3·3	3,600	136

* 2 pints (1·1 litres) of blood transfused before estimate.
† 3 pints (1·7 litres) of blood transfused after estimate (1).

TABLE III.—*Serum Chemical Analysis*

Date	Urea (mg./100 ml.)	Ca (mg./100 ml.)	Inorganic P (mg./100 ml.)	Uric Acid (mg./100 ml.)	Total Cholesterol (mg./100 ml.)	Alkaline Phosphatase (King-Armstrong Units)
Dec. 52	24					
May 53	22					
Aug. 54	22	9·2	3·7	5·5	170	5·2
Oct. 54	22	9·4	4·0		160	5·5
Oct. 55	21	9·3	3·5	5·4	170	4·5
Mar. 57	33*	—	—	—	—	—
Oct. 57	31	9·7	3·6	5·6	—	6·0
Dec. 57	29	9·7	3·6	5·5	—	6·0

* Maximum urea clearance value 78% mean of two successive periods.

treatment with blood transfusions and tetracycline was introduced. The patient made a satisfactory recovery from the agranulocytosis. In August she also received a short course of deep *x*-ray therapy to the spine. She was discharged from hospital with a spinal support in October. Results of electrophoretic and ultracentrifugal analysis at this stage are shown in Fig. B.

At the time of writing (March, 1958) she has all the clinical features of moderately advanced myelomatosis, and the course of the illness does not seem to have been influenced by radiotherapy or chemotherapy.

The principal biochemical and haematological findings are presented in Tables I–III.

Discussion

This case raises the interesting problem of the possible causes of hyperglobulinaemia and consequently raised E.S.R. According to Wintrobe (1956) the common causes are myelomatosis, lymphogranuloma venereum, sarcoidosis, disseminated lupus erythematosus, kala-azar, subacute bacterial endocarditis, cirrhosis of the liver, leukaemia, and chronic nephritis. To this list can be added "essential hyperglobulinaemia" as coined by Waldenström (1943, 1946, 1952), but the case for the existence of this condition does not seem to be fully established. Two of Waldenström's cases had macroglobulinaemia, which has now been shown by Martin and Close (1957) not to be a specific disease.

The finding of an increased number of plasma cells in the sternal marrow (13%) in December, 1952, certainly suggested myelomatosis as the correct diagnosis, because the upper limit of normal is usually regarded as being 1%–2% (Wintrobe, 1956; Whitby and Britton, 1957). A moderate increase in plasma cells, however, is not necessarily diagnostic of myelomatosis, as this may occur in rheumatic fever, collagen diseases, hypersensitivity reactions, cirrhosis of the liver, and Hodgkin's disease.

In myelomatosis *x*-ray changes in the bones are usually regarded as an essential feature, but it is now realized that a diffuse infiltration may occur without specific isolated lesions. Thus Wallerstein (1951) describes three such cases, and Kubota *et al.* (1956) found four in a series of 60 cases of proved myelomatosis.

The present case is described because such a long period (four years) had elapsed between the time when the patient was first known to have hyperglobulinaemia and the development of symptoms of clinical myelomatosis. During this time she seemed to be in normal health and carried out all her duties as a housewife. The only clinical abnormality was anaemia, which did not increase during this period (see Table II). Electrophoretic analysis showed marked increase in gamma-globulin, with the sharp peak characteristic of myeloma-globulin. Ultracentrifugal analysis showed an excess of proteins with an S_{20w} of 6.7, but no components of higher molecular weight. Another interesting point is that it was nearly five years before Bence Jones protein could be detected in the urine. This observation supports the suggestion of Putnam *et al.* (1956) that Bence Jones protein is not the direct result of degradation of the circulating or tissue proteins. It is also in accord with the now well-known fact that marked hyperglobulinaemia and Bence Jones proteinuria occur in inverse ratio (Snapper *et al.*, 1953). The pleural effusion which brought the patient under observation is presumed to have been tuberculous and not related to the subsequent development of myelomatosis, as no further chest complications have occurred and the chest has remained radiologically normal.

Summary

A case of myelomatosis is described in which four years elapsed between the discovery of marked hypergammaglobulinaemia and the development of signs and symptoms of this disease.

FOOTNOTE

The patient died on September 23, 1958. Necropsy confirmed the diagnosis of myelomatosis, there being extensive medullary and extramedullary deposits of plasma cells. There was moderate oedema of the lungs, but no evidence of tuberculosis.

One of us (N. H. Martin) wishes to acknowledge a grant from the free funds of St. George's Hospital, which enabled a portion of this work to be carried out.

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SUPPOSITORY TREATMENT OF HAEMORRHAGIC PROCTITIS

BY

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Haemorrhagic proctitis is a condition of unknown aetiology in which the rectum is diffusely inflamed. Other names for the condition are idiopathic proctitis and granular proctitis. If the inflammation extends into the sigmoid colon the condition is often referred to as proctosigmoiditis. The cardinal symptom is the passage of blood, pus, and mucus per rectum. There may be bouts of diarrhoea, but in between these the motions are usually firm or even costive. Indeed, some sufferers seldom or never experience diarrhoea. Rectal bleeding is more likely to be heavy when constipation is present, because of increased trauma during defaecation, and the blood is then separate from the main mass of the stool, not intimately mixed with it as in the diarrhoeal stool of classical ulcerative colitis. In between the passage of stools there are commonly several passages of blood or blood-stained mucus each day.

Lower abdominal pain may occur, low back pain is common, rectal pain is sometimes experienced, and tenesmus may be a feature; but the general health usually remains good and severe loss of weight and other signs of constitutional disturbance do not occur, with the conspicuous exception of anaemia. The anaemia is of the iron-deficiency type usually found in chronic blood loss and is sometimes severe. On sigmoidoscopy it is often possible to get above the

inflamed area and to observe normal colonic mucosa. The barium-enema examination is sometimes negative, although a skilled radiologist will usually detect an abnormal rectal mucosal pattern. In effect, the illness is a minor one compared with classical ulcerative colitis, in which the general health is often much affected and the disease sometimes runs a dangerous course.

Some workers regard haemorrhagic proctitis as entirely distinct from ulcerative colitis. For example, Hess Thaysen (1934) described it as "a morbid condition which, when present in a very mild degree, as a rule is mistaken for haemorrhoidal bleeding, while in its severe form it is usually regarded as ulcerative colitis, *although it has nothing to do with these two conditions*" (my italics). Similarly, Brooke (1953, 1954) distinguishes the condition of proctosigmoiditis from classical ulcerative colitis affecting a large part or the whole of the colon. Other authorities regard the condition as no more than ulcerative colitis which is localized to the rectum or to the rectum and the lower pelvic colon. Goligher (1953) stated that "it is certainly incorrect to describe ulcerative colitis and proctosigmoiditis as fundamentally different diseases." Among the reasons for this opinion he gave "our finding in a number of cases of mild granular proctosigmoiditis that the pathological process subsequently spread proximally to involve the entire colon and to produce severe symptoms requiring colectomy."

A study by Newell and Avery Jones (1958) revealed that 8% of patients with haemorrhagic proctitis when first seen had subsequently developed extensive ulcerative colitis. To quote their own words: "The view was firmly established from this survey that idiopathic proctitis was one and the same disease as ulcerative colitis but in a localized and milder form." My own experience is also strongly in favour of this view, for the following reasons: (1) Haemorrhagic proctitis has been observed to progress into extensive ulcerative colitis, exactly as described by Goligher and by Newell and Avery Jones. (2) Patients with classical ulcerative colitis have subsequently been seen with the symptoms and sigmoidoscopic signs of haemorrhagic proctitis. In some patients this has been merely a stage in the evolution of a severe attack of ulcerative colitis. (3) In the course of extensive biopsy studies of patients with rectal and colonic disease, now amounting to about 800 biopsy examinations, the histological appearances have proved to be similar in the two conditions.

There can therefore be little doubt that haemorrhagic proctitis is sometimes the precursor of ulcerative colitis and sometimes a sequel to an attack of it. We must inevitably conclude that, in at least some patients, haemorrhagic proctitis is merely a localized form of ulcerative colitis. The treatment of haemorrhagic proctitis therefore assumes importance for two distinct reasons: (1) the condition is troublesome and disagreeable to the patient and deserves to be treated on its own merits; and (2) if it can be successfully treated there is the possibility that some attacks of ulcerative colitis will be averted.

During recent years considerable success in treating ulcerative colitis has been obtained by the use of hydrocortisone solutions applied locally to the colon by means of a nightly rectal drip (Truelove, 1956, 1957). This form of treatment has been shown to be effective in a large proportion of patients by two independent studies each employing the "double-blind" technique (Truelove, 1958; Watkinson, 1958). Some of the patients included in my own studies have been examples of disease localized to the rectum and recto-sigmoid region, because I have never regarded this type of disease as basically different from more extensive ulcerative colitis.

The use of a nightly rectal drip has certain disadvantages in the case of patients with disease limited to the rectum and recto-sigmoid area. First, it involves some degree of inconvenience for the patient, which is a small price to pay if it relieves the symptoms of ulcerative colitis but is worth avoiding if equally good results can be obtained more simply. Secondly, a characteristic of the rectal drip is that the solution travels widely through the colon, a property which is unnecessary in the case of localized distal disease. Thirdly, the treatment involves the use of comparatively large quantities of hydrocortisone, so that long-term treatment is expensive.

Use of Suppositories in Treatment

In 1957 suppositories containing 10 mg. of hydrocortisone in the form of the hemisuccinate sodium ester were used to treat a case of post-radiation proctitis and were found to be highly successful. In consequence the use of these suppositories was extended to patients with distal forms of ulcerative colitis and proctitis. More recently, experience has been gained with suppositories containing prednisolone 21-phosphate, a compound resembling hydrocortisone hemisuccinate sodium in so far as it is highly soluble in water and would therefore be expected to enter the mucosa of the rectum and colon if brought into contact with it. The results with both these types of suppository have been encouraging, and the purpose of the present article is to present them.

Composition of the Suppositories.—Two types have been used. The first contains 10 mg. of hydrocortisone in the form of the hemisuccinate sodium ester which is incorporated in a base of oil of theobroma. The second contains 5 mg. of prednisolone 21-phosphate in a proprietary base.

Dosage.—Initially the suppositories were used twice a day, one being inserted at bedtime, the other after defaecation in the morning. In some patients in whom the response was excellent the dose was reduced after about three months to the nightly suppository only.

Results

The first 22 patients treated are now reported, brief individual details being given in Table I. Of these 22, 14 obtained complete relief from their symptoms, and this relief has persisted up to the time of writing, the suppositories having been discontinued in some of them or reduced to the use of one a day. In patients in whom the suppositories were effective the response was a decisive one, marked improvement occurring in the first few days, and the clinical response being complete in less than a fortnight. Favourable clinical responses were accompanied by corresponding improvement in the sigmoidoscopic appearances, which often became normal. In other words, if a definitely beneficial response is not apparent after two weeks at the outside, the suppositories can be considered to have failed and other therapeutic measures should be applied.

TABLE I.—*Clinical Details and Response to Suppository Treatment (the First 10 Cases were Treated with Hydrocortisone Hemisuccinate Suppositories, the Remainder with Prednisolone Phosphate Suppositories)*

Case No.	Sex and Age	First Attack or Relapse	Length of Immediate Symptoms	Total Length of History	Past History of Proctitis or Classical Ulcerative Colitis	Sigmoidoscopy before Treatment	Clinical Response	Sigmoidoscopy after Treatment	Subsequent Course	Length of Observation
1	M 37	F	3 months	3 months	—	Proctitis	Remission	Normal	Symptom-free	9 months
2	F 48	R	3 ,,	15 years	U.C.	,,	,,	,,	,,	9 ,,
3	F 17	F	4 ,,	4 months	—	,,	,,	,,	,,	9 ,,
4	M 22	R	1 month	11 years	U.C.	,,	Worse	Colitis	Other treatment	
5	F 42	R	1 ,,	6 ,,	P.	,,	Unchanged	Unchanged	,, ,,	
6	M 67	R	1 ,,	11 ,,	U.C.	Proctosigmoiditis	Improved	Improved	,, ,,	
7	F 23	R	2 years	2 ,,	P.	Proctitis	Remission	Normal	Symptom-free	7 months
8	M 30	R	6 weeks	1½ ,,	U.C.	,,	,,	,,	,,	7 ,,
9	M 23	R	4 months	2 ,,	P.	,,	,,	Near-normal	,,	7 ,,
10	F 32	R	1 month	5 ,,	P.	,,	,,	,,	,,	7 ,,
11	M 26	R	2 months	2 ,,	P.	,,	Unchanged	Unchanged	Other treatment	
12	F 36	F	11 ,,	11 months	—	Proctosigmoiditis	Remission	Normal	Symptom-free	6 months
13	M 37	R	1 month	11 years	P.	Proctitis	Unchanged	Unchanged	Other treatment	
14	M 25	F	1 ,,	1 month	—	,,	Remission	Near-normal	Symptom-free	6 months
15	F 31	R	1 ,,	1½ years	P.	,,	Unchanged	Unchanged	Other treatment	
16	F 41	R	1 ,,	5 ,,	U.C.	Proctosigmoiditis	,,	,,	,,	
17	M 47	R	2 months	3 ,,	P.	,,	,,	,,	,,	
18	M 34	R	2 ,,	9 ,,	P.	,,	Remission	Near-normal	Symptom-free	4 months
19	M 42	F	3 ,,	3 months	—	Proctitis	,,	,,	,,	4 ,,
20	F 40	F	8 ,,	8 ,,	—	,,	,,	,,	,,	4 ,,
21	F 23	R	1 month	3 years	U.C.	,,	,,	Normal	,,	4 ,,
22	F 78	F	2 months	2 months	—	,,	,,	Near-normal	,,	4 ,,

The finding that 14 out of 22 patients experienced symptomatic and sigmoidoscopic remission with the use of the suppositories makes the method of treatment appear moderately successful. A different slant is obtained by considering whether the cases were fresh ones or whether there was evidence of long-standing disease, either intermittent or continuous. Fresh cases have been defined as patients with symptoms beginning for the first time less than one year before suppository treatment was begun. When the patients are thus subdivided into fresh and chronic cases, an important finding emerges: *all the fresh cases responded well to the treatment.* All were symptom-free in less than a fortnight and with the sigmoidoscopic appearances either normal or near-normal. None of these fresh cases have relapsed up to the present time, although it must be mentioned that only two of them have ceased to use the suppositories. The uniformly successful results obtained with the fresh cases must be viewed with a certain reserve because there were only seven such cases (Nos. 1, 3, 12, 14, 19, 20, and 22), and from such a small sample any generalization should be made with caution. However, if we compare the results in these fresh cases with those obtained in the chronic ones, the results are significantly better for the former (Table II).

TABLE II.—*Comparison of Results of Treatment in Fresh and Chronic Cases of Haemorrhagic Proctitis*

	Effect of Treatment		Significance of Difference
	Failed	Successful	
Fresh cases ..	0	7	An exact test of significance gives a probability of approximately 0·04
Chronic ,, ..	8	7	

Further evidence about the type of case likely to be responsive to treatment can be sought by considering how successes and failures were distributed among the chronic cases. First, it does not seem to be important whether the previous history is of haemorrhagic proctitis or of classical ulcerative colitis. Thus there were six cases (Nos. 2, 4, 6, 8, 16, and 21) with a past history of more or less extensive ulcerative colitis, and three of these responded well; one of these three (Case 8) had previously had an extremely severe attack of ulcerative colitis with the whole colon involved. In other words, the extent of past involvement of the colon does not seem to influence the response to suppository treatment in those patients who relapse with the haemorrhagic proctitis syndrome.

Secondly, the length of the immediate attack of symptoms does not seem to be important, for most of the chronic cases had had their present symptoms for only a few weeks or months before starting treatment. It is the chronicity of the disease as a whole which marks off the chronic cases from the fresh ones, rather than the duration of the immediate symptoms. The conclusion to be drawn is that early diagnosis is of cardinal importance so that fresh cases are treated as they develop. If the bulk of these can be treated successfully there is at least the possibility that far fewer cases will evolve into the chronic form.

Illustrative Case Histories

Example of a Fresh Case (Case 1, Table I).—A man aged 37 was first seen in February, 1958, when he was referred by a surgical colleague because of haemorrhagic proctitis. For the previous three months he had been passing bright red blood on defaecation every day. A barium-enema examination had shown evidence of some abnormality in the mucosal pattern of the rectum and sigmoid colon but no evidence of neoplasm. Sigmoidoscopy revealed sharp inflammation of the rectum and recto-sigmoid area, with hyperaemia, granularity, and contact bleeding, but above 6 in. (15 cm.) from the anal margin these changes shaded off into normality. He was given the suppositories to use twice a day. After two days' treatment the rectal bleeding ceased and did not recur. Some mucus was passed per rectum for a few more days and he then became entirely symptom-free. Sigmoidoscopy carried out one month after starting treatment showed the rectal mucosa to be within normal limits. He has remained entirely symptom-free during the succeeding nine months, having stopped treatment after three months.

Example of Ulcerative Colitis Relapsing as Haemorrhagic Proctitis (Case 8, Table I).—A man aged 30 developed his first attack of ulcerative colitis in 1956. The attack became very severe, with involvement of the entire colon. He was given intensive in-patient treatment and eventually became symptom-free, although in the course of treatment he developed Heinz-body anaemia due to salicylazosulpha-

pyridine ("salazopyrin") therapy (he was Case 1 of the article dealing with Heinz-body anaemia by Spriggs *et al.*, 1958). Thereafter he remained entirely symptom-free until 1958, when he was seen in March with a six-weeks history of passing blood when the bowels were opened. Sigmoidoscopy showed the typical appearances of haemorrhagic proctitis. He was given suppository treatment. Improvement occurred after the first suppository, and in two days he became symptom-free. The sigmoidoscopic appearances were normal when he was examined one month later. During the succeeding seven months he remained clinically and sigmoidoscopically normal, the dose of suppositories having been reduced to one nightly after the first three months.

Discussion

The present study has shown complete symptomatic relief in two-thirds of the patients with haemorrhagic proctitis treated with suppositories containing water-soluble compounds of hydrocortisone and prednisolone. Symptomatic relief is accompanied by notable improvement in the sigmoidoscopic appearances, which become normal or close to it. This method of treatment cannot be expected to be effective against widespread colonic disease, and the ideal case for its use is one in which it is possible to get above the inflamed area on sigmoidoscopy. In any event, if there is no clear-cut satisfactory response in a fortnight, this method of treatment should be abandoned and some more powerful therapeutic approach tried. However, for those who respond favourably the method offers a treatment which is easy to apply and one which carries no appreciable risks of any side-effects. In such patients it seems at present desirable to continue with the treatment for some months, and ideally it should not be stopped unless the sigmoidoscopic appearances are normal. The slightest return of symptoms should be the signal for immediate resumption of treatment, because histological and sigmoidoscopic relapse precede clinical relapse, so that mild symptoms usually indicate the existence of sharp inflammation.

It should hardly be necessary to add that precise diagnosis is a *sine qua non* for the employment of this type of therapy, but observation of several examples of faulty diagnosis prompts the following remarks. Severe attacks of ulcerative colitis seldom present much difficulty in diagnosis in this country, although they may temporarily be attributed to an infective dysentery. The mildest cases, which include those now spoken of as haemorrhagic proctitis, have to be separated from two other common conditions. On the one hand, the rectal bleeding, which is so often the salient feature, may be attributed to haemorrhoids; this error does little harm because treatment of any haemorrhoids present fails to give relief and the diagnosis is then reconsidered. On the other hand, the symptoms of haemorrhagic proctitis are identical with those occurring in many examples of rectal and lower colonic carcinoma, and it is a tragic blunder if a patient is labelled as suffering from haemorrhagic proctitis (or simply from haemorrhoids) when in reality a carcinoma is responsible for the symptoms.

External examination of the anus is of little diagnostic help. Digital examination of the rectum is likewise of limited value, although it permits positive diagnosis of rectal growths which are low down. Sigmoidoscopy permits direct inspection of the rectal mucosa, and in most cases the diagnosis of haemorrhagic proctitis is immediately apparent when this is done; so also is the diagnosis of rectal and low colonic growths. A barium-enema examination should also be done to exclude a carcinoma or other lesions beyond the reach of the sigmoidoscope. That these elementary considerations deserve emphasis is apparent from a study by Muir (1956) from which it appears that the diagnosis of carcinoma of the rectum and colon is often unnecessarily delayed, the patient having symptoms for an average time of six months before he arrives at hospital. Similar findings by Swinton and Counts (1956) from America show that the problem is not confined to our own country.

With this proviso—namely, that the diagnosis of haemorrhagic proctitis has been confidently made on sigmoidoscopy and other lesions excluded by this examination and by barium enema—the use of the suppositories seems likely to bring relief to a large proportion of patients with the condition. This is especially likely to be so with fresh cases, for in these this treatment has so far proved uniformly successful.

Summary

Haemorrhagic proctitis is a disease of unknown aetiology in which the rectum is diffusely inflamed so that bleeding occurs spontaneously or with slight trauma, as, for example, during defaecation. If the inflammation extends into the sigmoid colon, the term proctosigmoiditis is employed. In our present state of knowledge it is best to regard haemorrhagic proctitis and proctosigmoiditis as localized distal forms of ulcerative colitis.

Suppositories containing water-soluble compounds of hydrocortisone and prednisolone have been used to treat 22 patients with the condition.

Rapid and complete symptomatic relief was obtained in 14 of these patients, such relief being accompanied by notable improvement in the sigmoidoscopic appearances, which usually became normal.

The best results were obtained in fresh cases of the condition, the treatment being uniformly successful in the seven patients of this type included in the series.

The treatment has the virtues of easy application and low dosage of steroids, so that side-effects are most unlikely to occur.

Some comments are made on the necessity for precise diagnosis before this form of treatment is used.

The hydrocortisone hemisuccinate suppositories were made in the pharmaceutical department of the United Oxford Hospitals. The prednisolone phosphate suppositories were made by Glaxo Laboratories. I am grateful to them both.

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Reviews

MUIR'S "PATHOLOGY"

Muir's Textbook of Pathology. Revised by D. F. Cappell, C.B.E., M.D., F.R.F.P.S., M.R.C.P., F.R.S.Ed. Seventh edition. (Pp. 1,201+xx; illustrated. 70s.) London: Edward Arnold Ltd. 1958.

It is a pleasure to welcome the seventh edition of Muir's "Pathology," which for thirty-four years has held its place in Great Britain as a sound, well-balanced, and wholly dependable textbook for the average medical undergraduate during his clinical training.

In a review of the first edition of "Muir," published in the *B.M.J.* in 1925 (April 25, p. 787), it was stated that:

> "'Ordered selection' used to be the principle that governed the Glasgow school of artists, and the same words could be used to describe briefly the method adopted in this product of the Glasgow school of pathology . . . we realize that the author has much in reserve, much more than he could have imparted . . . he has deliberately sacrificed this in order to preserve due balance."

By "ordered selection," critical omission, and skilful condensation it has been possible, without any undue increase in the size of the book, to include in six successive editions the very considerable advances in pathological knowledge which have been made during the last 30 years. If the wartime edition be omitted, the number of pages in each edition when plotted against time shows a steady straight-line relationship which if continued would produce in 1992 a volume twice the size of the first edition. This must be regarded as a sustained editorial achievement of some magnitude, but it is likely to call for even greater vigilance in the future if the actual weight of the book is to be kept within the limits imposed by the powers of mental digestion and assimilation possessed by the average undergraduate during his period of three years' intermittent reading.

Our reviewer described the first edition as "a sound and attractive view of the subject by a master who appreciates the fact that those whose interest is aroused will seek to learn more, and the awakening of the desire to learn more is the test of good teaching." We would venture to suggest that the limit of size of this undergraduate textbook has now been reached, and any further expansion is more likely to alarm the *average* student than to arouse his interest and awaken his "desire to learn more."

Professor Cappell's able revision of this and the preceding edition has covered several highly commendable modern developments in pathology which are directed to bridging the gap between the patient and his disease on the one side and the structural changes found in his diseased organs and tissues on the other. Of all modern developments in medicine this is of outstanding importance to the future relationship between pathology and clinical medicine. We find in the "Cappell" editions an increasing tendency to relate morbid anatomy and histology to age incidence, clinical course, signs, symptoms, clinical biochemistry, and haematology. A whole section, for instance, is devoted to fluid and electrolyte balance, and this is followed by a pithy discussion of the mechanism of the production of oedema, while, whenever relevant, modern views on the morbid physiology of disease are clearly explained in simple language. There is a new and up-to-date chapter on the aetiology of neoplasia, and another on the endocrine system. Neither of these chapters will upset the undergraduate mental digestion; both of them, models of clear exposition, reveal the imperfections of our present knowledge.

The additional illustrations in this edition number 100. The interpretation of many of the photomicrographs would be facilitated if the magnifications used were stated. A good deal of the information in small print could be omitted by the undergraduate, at least on first reading. The cover appears to be sturdy enough to carry the increased weight of the book, provided that it is handled with reasonable care and not too frequently used as a guided missile.

GEOFFREY HADFIELD.

DISINFECTION AND STERILIZATION

Disinfection and Sterilization. By G. Sykes, M.Sc.(Lond.), F.R.I.C. (Pp 396+xviii; illustrated. 75s.) London: E. and F. N. Spon, Ltd. 1958.

This book follows the conventional lines of a work on the general subject of how to destroy microbes. Theories of disinfection and methods of testing disinfectants are followed by sterilization by heat, radiation, filtration, and other physical means. Chemical disinfectants themselves are considered in only five chapters under the headings of phenols, soaps, and alcohols; dyes; quaternary ammonium compounds; halogens; and heavy metals. Only three applications are separately considered—the disinfection of air, the destruction of viruses, and preservation and preservatives; many other uses are mentioned only incidentally in descriptions of the properties of individual disinfectants. These are admirably full and informative, and no better account of the theoretical aspect of this subject has been written. The hygienist will also find most of the background information he needs for many applications in industry and the field of public health. Clinical applications are less well catered for, apart from a good deal of information about skin disinfection; and some very odd uses are mentioned with no suggestion that they are now abandoned or discredited, including the application of calomel or silver picrate to wounds and the parenteral administration of halogenated phenols for the treatment of "urogenic" infections.

The book is very sparsely illustrated, and gives the impression of having been written some years ago; there is no mention of chlorhexidine, urea derivatives, the nitrofurans, or the new ampholytic surface-active compounds. Although there are gaps in its usefulness to the medical reader, we should be grateful that someone in this country has at last produced an otherwise worthy book on this very large and difficult subject.

L. P. GARROD.

CLINICAL HAEMATOLOGY

Clinical Haematology in Medical Practice. By G. C. de Gruchy, M.D.(Melb.), F.R.A.C.P., M.R.C.P.(Lond.), M.C.P.A. (Pp. 620+xii; illustrated. 50s.) Oxford: Blackwell Scientific Publications. 1958.

There has been need for a book on haematology which gives more information than is provided by the text-books of general medicine and yet is not so encyclopaedic as "Wintrobe" or "Whitby and Britton." It can now be said that the New World has come to redress the balance of the Old with this book by

Dr. de Gruchy, who is physician in charge of the Haematology Clinical Research Unit at St. Vincent's Hospital, Melbourne, a city which has a flourishing group of haematologists. As befits an Australian author, his outlook is pragmatic, with emphasis on the clinical aspects of blood disorders, diagnosis, and management of the patient; details of technical methods are deliberately omitted. The first two chapters deal with blood formation, the bone marrow, the red cell, and the pathological physiology of anaemia. The various blood disorders are then discussed seriatim in the remaining 13 chapters.

Dr. de Gruchy has managed to arrange the heterogeneous material of haematology in an orderly sequence—the anaemias, the disturbances of the white cells, the hyperplastic disorders, the splenomegalies, the haemorrhagic diseases, disorders of pigment metabolism, and blood groups and transfusion. The writing is clear and the information up to date, and Dr. de Gruchy is to be congratulated on giving a balanced account of the diseases of the blood in 600 pages. The book is strongly recommended to those who wish to obtain a firm grounding in haematology. A review can rarely be all praise. One regrets the absence of coloured pictures; perhaps they are expensive, but this is like reading a travel book without a map. It is possible, also, that Dr. de Gruchy has been almost too practical and pragmatic; will the novice realize what exciting subjects intrinsic factor and glutathione are to workers in haematological laboratories?

L. J. WITTS.

A SUCCESSFUL MASQUERADE

The Strange Story of Dr. James Barry, Army Surgeon, Inspector-General of Hospitals, Discovered on Death to be a Woman. By Isobel Rae. (Pp. 124+vii. 13s. 6d.) London, New York, Toronto: Longmans, Green and Co. 1958.

The story of Dr. James Barry has been told many times and has even been woven into fiction, but it has never been so accurately or so interestingly told as by Miss Isobel Rae. How came it that a woman should qualify as a doctor, serve as a surgeon in the Army, and rise to the rank of Inspector-General of Hospitals without detection of the masquerade? Miss Rae has done an excellent piece of historical research, and by her sleuth-like methods has converted a plain tale into a first-rate piece of detection.

Dr. Barry was professionally clever, hard-working, conscientious, and eager to reform abuses; this brought her up against routine authority, but, like Miss Nightingale, Miss Barry often wrote over the heads of her immediate superiors to the highest authority in order to get her way—an efficacious but not altogether popular method. It is remarkable, indeed, that she performed one of the earliest successful caesarean sections—upon a lady called Munnik; one of the caesarean baby's children was godparent to James Barry Munnik Hertzog, who became Prime Minister of South Africa.

There were some who suspected that Dr. Barry was a woman, but the fact was not proved till after her death. Some of her habits must have given rise to comment. She was a teetotaller, a strict vegetarian, had a black servant as bodyguard, and always kept a little dog which ate its master's ration of meat and was called Psyche—a significant name. Dr. Barry died on July 29, 1864, at 14, Margaret Street, Marylebone, in her seventieth year, but there is no plaque on the building to indicate this.

ZACHARY COPE.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

Symposium on Gastroduodenal Ulcer and Cancer. International Study among the Black, Bronze, White, Yellow, Aztec, Bantu, Basa, Bedouin, Esquimo, Maori, Red-Skin Indian, Yaqui, Zapotecan Peoples. Volume II, in two parts. By Prof. Dr. William Nimeh, F.A.C.P. (Pp. 182+xii; illustrated.) Beirut: Publications de l'Université Libanaise. 1958.

Advances in Virus Research. Edited by Kenneth M. Smith and Max A. Lauffer. Volume VI. (Pp. 382. $10.) New York: Academic Press Inc. London: Academic Books Ltd. 1959.

Traitement des Suppurations Urétro-Génitales et de Leurs Complications chez l'Homme et chez la Femme. By Pierre Durel and André Siboulet. (Pp. 168; illustrated. 2,100 fr.) Paris: G. Doin et Cie. 1959.

The Anatomy of the Nervous System. Its Development and Function. By Stephen Walter Ranson, M.D., Ph.D. Revised by Sam Lilliard Clark, M.D., Ph.D. 10th ed. (Pp. 622+xii; illustrated. 66s. 6d.) Philadelphia, London: W. B. Saunders Company. 1959.

Hormones and Atherosclerosis. Proceedings of the Conference Held in Brighton, Utah, March 11-14, 1958. Edited by Gregory Pincus. (Pp. 484+xvi; illustrated. $13.50.) New York: Academic Press Inc. London: Academic Books, Ltd. 1959.

Clinical Neurosurgery. Proceedings of the Congress of Neurological Surgeons, Washington, D.C., 1957. Volume 5. (Pp. 206+xix; illustrated. 64s.) Baltimore: Williams and Wilkins Company. London: Baillière, Tindall and Cox Ltd. 1958.

The Ecology of Human Disease. By Jacques M. May, M.D. Foreword by Felix Marti-Ibañez, M.D. (Pp. 327+xxi. $7.50.) New York: MD Publications, Inc. 1959.

William Harvey's De Motu Locali Animalium, 1627. Edited, Translated, and Introduced by Gweneth Whitteridge, M.A., D.Phil., F.S.A. (Pp. 163+x. 60s.) Cambridge: Published for the Royal College of Physicians, at the University Press. 1959.

Bleeding Esophageal Varices. Portal Hypertension. By Hirsch Robert Liebowitz, B.S., M.D. Section on Surgical Treatment in Collaboration with Louis M. Rousselot, M.D., M.S.(Surg.), Med.Sc.D.(Surg.), F.A.C.S. (Pp. 986+xxxiii; illustrated. £9 3s. 6d.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

Epilepsy. By Manfred Sakel, M.D. With a preface by Otto Poetzl. (Pp. 204+xxxvi. 35s.) London: Peter Owen. 1959.

Battle for the Mind. A Physiology of Conversion and Brain-Washing. By William Sargant, 3rd ed. (Pp. 134; illustrated. 2s. 6d.) London: Pan Books Ltd. 1959.

Clinical Neurophysiology. By John Marshall, M.D., F.R.C.P.(Ed.), M.R.C.P., D.P.M.(Lond.). (Pp. 296+viii; illustrated. 37s. 6d.) Oxford: Blackwell Scientific Publications. 1959.

The Rewards of Medicine and Other Essays. By Hugh Barber. (Pp. 140. 15s.) London: H. K. Lewis and Co. Ltd. 1959.

Psychopharmacology Frontiers. Second International Congress of Psychiatry, Proceedings of the Psychopharmacology Symposium. Edited by Nathan S. Kline, M.D. (Pp. 533+xxiii. 72s.) London: J. and A. Churchill Ltd. 1959.

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INTIMAL HAEMORRHAGE

Intimal haemorrhage has long been recognized as an occasional feature of atherosclerosis, but credit for the recognition of its importance goes to J. C. Paterson.[1] In 1936 he recorded its occurrence in nine consecutive cases of coronary thrombosis and suggested that it was the factor responsible for the thrombosis. In this and a subsequent communication[2] he showed that the haemorrhages arose from rupture of capillaries which were present in atherosclerotic plaques, and he stressed the point that some of these capillaries were in direct communication with the lumina of the affected arteries and might therefore be exposed to an especially high blood pressure.

The presence of vascular channels in atherosclerotic plaques, especially of the aorta, has been known since the middle of last century, but the first detailed account was supplied by M. C. Winternitz, R. M. Thomas, and P. M. Le Compte in their monograph[3] published in 1938. They demonstrated that the atherosclerotic intima was permeated by vascular channels both from the lumen of the artery and from the vasa vasorum, and they regarded this as a factor in the development of atherosclerosis. They showed that haemorrhage frequently occurred from these vessels, and they made the important suggestion that much of the fatty debris in the atheromatous foci was the product of degeneration of the extravasated blood. This was a bold departure from the current belief.

Other workers have since studied intimal haemorrhage but have differed on its importance. W. B. Wartman,[4] H. Horn and L. E. Finkelstein,[5] and M. G. Nelson[6] considered that it was a significantly frequent feature of fatal coronary disease, Wartman believing it to be the main factor in coronary occlusion, since by increasing the thickness of the intima it constricted the lumen of the artery. Paul Wood,[7] on the other hand, was inclined to doubt its frequency, while J. P. English and F. A. Willius,[8] and more recently R. A. B. Drury,[9] admitted its frequency but regarded it as of secondary importance. Nevertheless, there has in recent years been a growing appreciation of its significance not only in coronary disease but in atherosclerosis in general.

In 1946 and 1948 J. B. Duguid[10 11] showed that some of the intimal thickenings which had hitherto been interpreted as overgrowths of connective tissues were in reality organized mural thrombi. He also noted that in the process of organization such thrombi were sometimes invaded by capillaries both from the lumen of the artery and from the vasa vasorum, and that these vessels, remaining long after the organization was completed, accounted for much of the vascularization of the intima. His observations were confirmed by E. Geiringer[12] and N. G. B. McLetchie,[13] both of whom emphasized that capillaries connecting with the lumen were characteristic of mural thrombi. Similar evidence has lately been produced by J. H. Dible.[14] A. D. Morgan[15] has confirmed these findings, together with the findings of Paterson on intimal haemorrhage. He showed that many of the capillaries in the atheromatous plaques passed into the softened areas, and, being poorly supported, were prone to rupture; like Winternitz and colleagues, Morgan believed that when this occurred the extravasated blood was converted into atheromatous debris.

Somewhat later Duguid and W. B. Robertson,[16] reviving the mechanical theories of the older writers, suggested that intimal haemorrhages were the result of the functional movements of arteries. In atherosclerosis, according to them, the stiffened intima, being unable to participate with the rest of the tissues in the pulse movements of expansion and recoil, becomes loosened and partially torn away from the media. Intimal vessels are liable to be torn, and these workers considered that haemorrhage as a result of this was common. Like Morgan they also believed that the repeated extravasation of blood accounted for much of the atheromatous change.

In the last few years Paterson and his co-workers have with improved techniques reverted to the problem of intimal haemorrhages. They were able to show[17] that unsuspected intimal haemorrhage could be brought to light by the Prussian-blue reaction

[1] Paterson, J. C., *Arch. Path.* (*Chicago*), 1936, **22**, 313.
[2] —— ibid., 1938, **25**, 474.
[3] Winternitz, M. C., Thomas, R. M., and Le Compte, P. M., *The Biology of Arteriosclerosis*, 1938, Baltimore.
[4] Wartman, W. B., *Amer. Heart J.*, 1938, **15**, 495.
[5] Horn, H., and Finkelstein, L. E., ibid., 1940, **19**, 655.
[6] Nelson, M. G., *J. Path. Bact.*, 1941, **53**, 105.
[7] Wood, P., *Diseases of the Heart and Circulation*, 1950, p. 704, London.
[8] English, J. P., and Willius, F. A., *Arch. Intern. Med.*, 1943, **71**, 594.
[9] Drury, R. A. B., *J. Path. Bact.*, 1954, **67**, 207.
[10] Duguid, J. B., ibid., 1946, **58**, 207.
[11] —— ibid., 1948, **60**, 57.
[12] Geiringer, E., ibid., 1951, **63**, 201.
[13] McLetchie, N. G. B., *Amer. J. Path.*, 1952, **28**, 413.
[14] Dible, J. H., *J. Path. Bact.*, 1958, **75**, 1.
[15] Morgan, A. D., *The Pathogenesis of Coronary Occlusion*, 1956, Oxford.
[16] Duguid, J. B., and Robertson, W. B., *Lancet*, 1957, **1**, 1205.
[17] Paterson, J. C., Moffatt, T., and Mills, J., *Arch. Path.* (*Chicago*), 1956, **61**, 496.
[18] —— Mills, J., and Moffatt, T., ibid., 1957, **64**, 129.
[19] Mills, J., Moffatt, T., and Paterson, J. C., *Lab. Invest.*, 1958, **7**, 606.
[20] Moffatt, T., ibid., 1958, **7**, 544.
[21] Aschoff, L., *Lectures on Pathology*, 1924, New York.
[22] Allbutt, Sir Clifford, *Diseases of the Arteries including Angina Pectoris*, 1915, London.

applied to gross segments of unfixed arteries. By this method haemosiderin was seen to be plentiful, even in early atherosclerotic lesions. Using the alkaline phosphatase technique for the staining of endothelium, they demonstrated[18] that capillaries were present in hitherto unsuspected numbers in early lesions, and they implied that vascularization was a fundamental factor in the disease process.

Now these workers,[19] using a special clearing technique described by Moffatt,[20] have shown that the incidence of intimal haemorrhages in the aorta is greater in hypertensive patients than in others; and again they have invoked the factor of high blood pressure in capillaries connecting with the lumen of the artery to explain it. They mention other factors, it is true, such as defective support of tissues and capillary fragility, but no reference is made to the increased pulse movements which, as Duguid and Robertson suggested, must come into play in hypertension. The high pulse pressure in this condition must increase the range of the pulse movements, and all the strains and tearing forces to which the artery walls are subjected must be accentuated. It is not surprising, therefore, that, when there are delicate capillaries in the intima, haemorrhages should result.

Paterson and his colleagues also believe that the haemorrhages contribute to the accumulation of lipids, so that they regard haemorrhage not only as the factor promoting terminal coronary thrombosis but also as an accelerating factor in atherosclerosis itself. They remark that "if the extravasated blood contains a high concentration of lipid, more lipid should be deposited than when the serum lipid levels are low," which goes a long way in supporting Aschoff's contention that "the lipoid concentration of the food does not cause atheroma, but essentially influences the character of the atheromatous patches by determining the presence or absence of fatty change."[21] Perhaps the time will come when opinion veers around again to the old wear-and-tear concept of atherosclerosis, so strongly advocated by Sir Clifford Allbutt.[22]

DOSE OF ACCIDENTAL RADIATION

In October, 1957, there was a fire in the Windscale No. 1 reactor in Cumberland, and radioactivity, chiefly the volatile fission products, escaped from the exhaust stack to be deposited down-wind.[1,2] Permissible doses for workers under conditions of emergency or accident have been considered by the International Commission on Radiological Protection (I.C.R.P.). and agreed, though not yet formally published. But there were no universally accepted permissible doses for an emergency like this affecting a population, albeit a small one, not occupationally exposed to radiation. Such permissible doses are readily calculable and were in fact used as a guide to action forthwith, but it is appropriate that the doses worked to in this incident should receive critical evaluation and if possible be codified. It is with this problem that the Medical Research Council's Committee on Protection against Ionizing Radiations, under the chairmanship of Dr. E. E. Pochin, has lately been concerned, and their report is published in the *Journal* this week at p. 967.

First, the Committee considers that, for the population living at the scene of the accident, the limiting hazard will generally be internal irradiation due to ingestion of local food substances contaminated with fission products rather than from inhalation. This is readily understandable. The radioactive cloud is non-persistent, but any radioactivity deposited persists for varying lengths of time, depending on physical and biological phenomena. As is the case with fall-out from weapons, irradiation from radio-isotopes within the human body is likely to be more significant than radiation from outside it, because the cow by its grazing habits acts as a scavenger of the radioactivity deposited on pasture and we depend in Britain on milk as a source of food. Therefore this report deals with those fission products which are of high yield in fission, readily absorbed from the gut, and, with the exception of the first, long-lived—namely, iodine-131, strontium-89, strontium-90, and caesium-137. Iodine and strontium are furthermore concentrated in particular tissues.

Secondly, though permissible dosage of strontium-90 is discussed on the basis of the dose-rate of radiation that will result from the retention for many years in bone of a fraction of the amount ingested, the other radioactive isotopes are considered from the aspect of the total dose of radiation they will give during their whole life of some months only in the various tissues. This perhaps will be a somewhat new concept for many who have been used to thinking and working in terms of permissible dose-rates, but in fact there is much more basic and practical experience with total doses than with dose-rates. In the experimental field almost the whole of our knowledge is confined to the effects of radiation either to the whole body or to part of an animal resulting from single doses or short courses of radiation, while in clinical medicine we are accustomed to measure doses of radiation for therapy or diagnosis. We can thus have considerable confidence in this new mode

[1] *Brit. med. J.*, 1957, 2, 991.
[2] Ibid., 1957, 2, 1166.

of expression. The report suggests levels which are intended to apply to numbers of people small compared with the whole population of the United Kingdom. In this respect it follows the principles of the I.C.R.P.'s recommendations.

Where the Medical Research Council's Protection Committee takes a new line is over strontium-90. The concentrations rated as permissible—1,000 strontium units (S.U.) for the occupationally exposed (the I.C.R.P. figure) and 100 S.U. for members of the general population—were based on the relative doses, for acute toxicity, given by the proportion radium-226 : strontium-90 = 10 : 1. There are now data to indicate that for chronic toxicity the ratio is about 50 : 1, which is what one would predict from the calculations of respective dose-rates. The committee has therefore made for consistency and founded its permissible figures for strontium-90 as for other chronic radiation hazards on dose-rate. It has followed the line of the I.C.R.P., regarding for small populations 10% of the dose for the occupationally employed as the maximum permissible. This means 1.5 rads per year for bone cells. Under the worst conditions this is equivalent to the dose-rate from areas of bone contaminated at the level of 500 S.U.—that is, 500 $\mu\mu$c per gramme of calcium. What the committee virtually says is that even small areas of bone can become contaminated to this level only when the intake reaches about 2,000 $\mu\mu$c of strontium-90 a day, on the assumption of a daily dietary intake of 1 g. of calcium, which is about the average normal for persons of all ages in Great Britain.

When one considers the other isotopes concerned, the permissible doses found in these special circumstances are for the thyroid (iodine-131) 25 rads, for bone-cells (strontium-89) 15 rads, and for virtually the whole body (caesium-137) 10 rads. These figures are roughly the same as what may be regarded as permissible during any one year for an occupationally exposed person who can continue to be exposed at or around this level for a generation or more. The equation therefore is to be considered between the non-occupationally exposed person, who may be a juvenile and subjected to this irradiation for a matter of months only, and the occupationally exposed adult, who may be exposed at a comparable level for many years. Neither should show any ill effect.

What could be at first sight surprising is that no distinction is apparently drawn between the infant or juvenile in the environment and the adult. The distinction can be observed in practice rather than theory. The committee, taking into account the appropriate metabolic data, has calculated the maximum permissible daily intakes (in mμc per day) of each of these radioactive substances to give the maximum permitted doses to the tissues of infants, juveniles, and adults. The obvious result is that the permissible intake increases with age ; but the various articles of diet are not consumed in the same ratios by infant, juvenile, and adult. For instance, the infant drinks as much milk as the adult and milk is the food most likely to set the limit. Therefore, in practice, concentrations of the respective radioactive substances in foods will be determined by the tolerance of the young.

VENOUS SHUNTS IN CIRRHOSIS OF THE LIVER

In the last decade many articles have appeared on the value of venous shunts in patients who suffer from oesophageal varices. Such varices are of frequent occurrence in cases of portal hypertension, whether the underlying cause is intrahepatic, as in cirrhosis of the liver, or extrahepatic, as in thrombosis of the splenic vein. Cirrhosis of the liver is the most frequent cause of portal hypertension. The practical importance of oesophageal varices is that they are apt to be the source of heavy bleeding, which is often fatal. It is this fact which has stimulated surgeons throughout the world to carry out operations designed to get rid of them. The two chief operations are portacaval anastomosis, when the portal vein is joined to the inferior vena cava, and spleno-renal anastomosis, in which splenectomy is carried out and the splenic vein is joined to the renal vein. Sufficient time has now elapsed for some tentative judgments to be formed on the value of these procedures, and, so far as cirrhotic patients are concerned, M. M. Nachlas has published a critical evaluation which deserves attention.[1] His method was to ask a number of highly pertinent questions and answer them from information recorded in the literature.

The first question is whether portal hypertension is the cause of variceal haemorrhage, and Nachlas concludes that it is not the sole factor responsible. It also appears problematical whether the raised hydrostatic pressure in the oesophageal varices can be regarded as solely responsible for the haemorrhage. Since most patients with varices have pressures of 300–400 mm. of water in the varices, it is difficult to see why massive haemorrhage should occur from them rather than from the veins of the haemorrhoidal plexus, which sustain a pressure of 600 mm. or more

[1] Nachlas, M. M., *Ann. Surg.*, 1958, **148**, 169.
[2] Taylor, F. W., and Egbert, H. L., *Surg. Gynec. Obstet.*, 1951, **92**, 64.
[3] Summerskill, W. H. J., Davidson, E. A., Sherlock, S., and Steiner, R. E., *Quart. J. Med.*, 1956, **49**, 245.
[4] Reynell, P. C., *Lancet*, 1951, **2**, 383.
[5] Hunt, A. H., *Portal Hypertension*. Livingstone, Edinburgh, 1958.

when the subject is erect. Nachlas agrees with the view by F. W. Taylor and H. L. Egbert,[2] who doubt whether "a rise of 100 or 200 mm. in portal pressure could alone be responsible for varices and massive haemorrhages." It also appears that in many patients a venous shunt operation does not produce sufficient lowering of the portal pressure to do away with the oesophageal varices; they persist, though often smaller, in 60% of the patients operated on. The operation itself carries considerable risk, and approximately 20% of patients with cirrhosis die from it. There is also evidence that the cirrhotic liver may be further damaged by diverting away from it the portal blood. Moreover, the neuropsychiatric syndrome of liver disease may be a sequel of shunt operations.[3] Finally, Nachlas questions whether there is any evidence to suggest that the carrying out of a venous shunt improves the prognosis of patients with cirrhosis of the liver. From published data he constructs a comparative picture of the results of medical and surgical treatment in an imaginary group of 200 cirrhotic subjects who suffer from haemorrhage due to varices. The first bleed is likely to kill 100 of them. The remaining 100 he pictures as divided between medical and surgical treatment and he estimates that there will be 35 of the medically treated patients alive at the end of a year compared with 32 of the surgically treated ones. He concludes: "Although one derives no satisfaction in pointing out our failures, this effort will be considered worthwhile if it prevents patients from being subjected in the future to a procedure of great risk and questionable benefit."

One of the difficulties in assessing surgical treatment for cirrhosis is that patients with signs of severe liver failure are often excluded from surgery. In other words, the surgeon is most likely to operate on patients who have varices but not severe ascites or jaundice. But it has been shown that the prognosis of bleeding from oesophageal varices is intimately related to the state of the liver, being relatively good in those without evidence of severe parenchymal disease.[4] Thus the surgeon is likely to choose patients for operation whose prognosis is in any case not particularly bad. This is worth bearing in mind before dismissing Nachlas's arguments as mere iconoclasm. Other evidence suggesting that he is not necessarily unduly pessimistic comes in the monograph by A. H. Hunt.[5] Among 60 patients with advanced cirrhosis not operated on there were 47 deaths (78%), while among 50 patients treated surgically there were 42 deaths (84%). Among the patients treated surgically, the best results were obtained from portacaval anastomosis, but even in this group of 23 patients there were 16 deaths (70%).

OSTEOMALACIA

Osteomalacia, or adult rickets, is a disease of the skeleton in which new osteoid tissue fails to calcify properly as it is laid down. In this it differs from osteoporosis, which is simply a reduction in the amount of bone present. The longer osteomalacia persists, the larger becomes the proportion of uncalcified collagen in the skeleton, and the weaker and softer the bones become until pains in the bones, fractures, or muscular weakness (which has never been fully explained) bring the patient to the doctor.

The diagnosis of the condition is not unduly difficult. Even if the characteristic Looser zones are not present in the limbs, *x*-ray examination will show diffuse decalcification, particularly in the peripheral bones. Biopsy of the iliac crest, which should preferably be cut for microscopical examination without decalcification, reveals the pathognomonic large osteoid borders. But, above all, it is the biochemical changes in the plasma which usually enable the diagnosis to be made and also hold the clue to the pathogenesis of the disorder. These changes are a reduction in the levels of calcium and phosphate—a low product of calcium × phosphate—and a high alkaline phosphatase.

There can be little doubt that in simple osteomalacia it is the reduction in the plasma Ca × P product which is responsible for the failure of new bone to calcify. It is significant that rachitic rat cartilage will calcify in normal plasma or in synthetic solutions containing corresponding concentrations of calcium and phosphate, but will not calcify in rachitic plasma or in synthetic solutions containing low levels of calcium and phosphate.[1] It is also clear that osteomalacia is usually due to lack of vitamin D, though at present this is more commonly the result of malabsorption than of dietary deficiency. But it is not altogether clear why lack of vitamin D reduces the plasma Ca × P product. In the *Journal* this week Professor F. S. P. van Buchem reviews (p. 933) the causes and types of osteomalacia, and supports the concept that the reduced phosphate level in the plasma in cases of osteomalacia is the result of secondary hyperparathyroidism. He accepts the orthodox view that this parathyroid overactivity is the result of a fall in plasma calcium due to poor absorption from the gut, the role of vitamin D in calcium absorption being well established.

Of relevance here is the work of A. Carlsson and B. Lindquist on the "calcaemic" action of vitamin D.[2] These workers showed, in confirmation of a prophetic statement by F. C. McLean,[3] that vitamin D can raise the plasma level of calcium in rachitic animals by an action directly upon the skeleton, and their work implies that deficiency of vitamin D could lead to a fall in the plasma calcium owing to the absence of this action upon bone.

Though the idea that malabsorption of calcium secondary to deficiency of vitamin D causes osteomalacia is generally held, increasing knowledge of the dynamic equilibrium which exists between the

[1] Yendt, E. R., Connor, T. B., and Howard, J. E., *Bull. Johns Hopk. Hosp.*, 1955, **96**, 1.
[2] Carlsson, A., and Lindquist, B., *Acta paediat.* (*Uppsala*), 1955, **44**, 548.
[3] McLean, F. C., *J. Amer. med. Ass.*, 1941, **117**, 609.
[4] *Brit. med. J.*, 1959, **1**, 495.

calcium in the plasma and the calcium in the skeleton strongly suggests that factors affecting this equilibrium are more likely to modify the plasma level of calcium than are changes in the relatively small amount of calcium normally absorbed from the gut.

The other types of osteomalacia described by van Buchem are rare and the status of some of them is rather doubtful. One of these is a condition which the Boston School have termed idiopathic hypercalciuria, but, as has recently been pointed out in these columns,[4] the causal relationship between hypercalciuria and osteomalacia is far from established. Van Buchem is the first to suggest that the skeletal complications of prolonged steroid therapy—which have not yet received the thorough study they deserve—can take the form of osteomalacia rather than osteoporosis. Further investigation, including in particular the histological examination of the bone in affected cases, would be welcome to confirm or reject this novel idea.

ESCAPE FROM SINKING AIRCRAFT

Ditching has always been a major hazard to those who fly over the sea, and the risk has not lessened proportionately with advances in aviation. On the contrary, it is now a very serious one—particularly to the pilots of jet aircraft of the fighter type engaged in carrier-based operations. A large airliner may, in favourable circumstances, alight fairly gently on the sea and remain afloat long enough for the passengers to board dinghies in an orderly way and await rescue. Unfortunately, this is not true of modern military aeroplanes. These tend to sink very quickly in water because of the weight and complexity of the engines, armaments, and equipment, which leave little buoyant space at all within the aircraft. The serious concern of the Royal Navy, especially, stimulated by a survey showing that up to 1954 30% of aircrew involved in any kind of ditching did not survive,[1] led to research into the practicability of using the ejection seat to escape from submerged aircraft. Ironically, such an escape was demonstrated for the first time in October, 1954—on the day after a meeting at which the possibility had been denied by expert opinion.

The frequency with which people are trapped and drowned in sinking motor-cars illustrates the difficulty of scrambling out of a confined space amid panic and the inrush of water, when they are hampered also, perhaps, by injury. In aircraft the difficulties are greater. The cockpit canopy may be locked and the pilot strapped tightly into his seat. If the aircraft ditches and sinks before he can open the canopy and climb out, his situation is grave. The canopy is held fast by the differential pressure of the water, which rises by approximately one atmosphere for every 33 ft. (10 m.) in depth. The pilot will have to wait until the cockpit has "flooded-up" to a differential pressure favourable for jettisoning the canopy. If the rate of sinking is disproportionately greater than the rate of flooding-up, the canopy may cave in, or the aircraft sink too deep for successful escape.

The physiological reactions to under-water ejection need careful evaluation. The most important factors are the response of the body to hydrodynamic drag, the pressure-wave from the ejection gun, and the risk of burst lung due to rapid ascent. The last hazard increases with depth of ejection and is familiar to everyone concerned with diving and submarine escape. The reliability of the ejection gun in water has also had to be investigated, as well as the practicability of ejecting through the cockpit canopy.

During seat-ejection in air the acceptable limit of thrust is determined by the rate of onset of the acceleration and by its peak value.[2] Drag is negligible during this phase of the escape. In water, the acceleration of the seat is lower, but the hydrodynamic drag induced in reaching speeds of up to 35 ft. (11 m.) per sec. imposes a considerable flexion load upon the man. These forces, although acceptable in the circumstances, approach the maximum tolerable. A pressure-wave generated by the detonation strikes the abdomen and chest. Although severe, this dynamic pressure has been said to have a beneficial action in assisting the expulsion of air from the lungs before ascent.[3] It cannot, however, be assumed to be sufficient alone in all cases.

Pulmonary barotrauma must be an accepted risk in under-water ejection. A seat fired at a moderate depth, say 30 ft. (9 m.), will rise about 15 ft. (4.5 m.), thus reducing the ambient pressure by half an atmosphere. As in submarine escape, a too rapid ascent, which denies the free exit of expanding air from the lungs, may result in mediastinal emphysema, pneumothorax, and air embolism. They can occur in healthy individuals, but there is some evidence that these conditions—and air embolism in particular—are more likely to develop in association with pre-existing pulmonary abnormality, albeit subclinical.[4 5] To prevent damage to lungs, the Navy is giving aircrew a practical course of instruction in the breathing techniques used in submarine escape: they are taught to breathe out both on ejection and throughout the ascent. It is thought that escape by ejection seat should be possible at depths of at least 100 ft. (30 m.) Ejection is not recommended if conventional escape is at all practicable, or if the aircraft is still within a few feet of the surface. In this case there is a danger that the man and the seat may follow a trajectory through the air and fall heavily into the sea without separation. Under-water ejection has saved life. Although it is a violent procedure, it will undoubtedly save life again in the future.

HEALTH SERVICE ESTIMATES

The budgeted cost of the Health Service in the new financial year cannot be compared with its cost in previous years because from the total there has now been omitted the Exchequer's grants to local authorities in respect of the local health services. Instead of the specific grants borne on the votes of the various Ministries, which in the case of the Health Service amounted to 50% of the cost of the services provided by the local health authorities, the Exchequer is giving

[1] Rawlins, J. S. P., *Proc. roy. Soc. Med.*, 1958, **51**, 828.
[2] Latham, F., *Proc. roy. Soc., B*, 1957, **147**, 121.
[3] Beckman, E., McNutt, D. C., and Rawlins, J. S. P., *Air Ministry Flying Personnel Committee Report No. 1049*, 1958.
[4] Duffner, G. J., *A.M.A. Arch. Industr. Hlth*, 1958, **18**, 208.
[5] Lambert, R. J. W., *Proc. roy. Soc. Med.*, 1958, **51**, 824.

this year a general grant, amounting to around £500m. in total. Thus local councillors are being left to decide how much of their share of this grant, together with what they can raise from the rates, they will allocate to the different services. In the first ten years of the Health Service the cost of the local authority services had risen from around £30m. to around £60m.—part of this increase being due to higher prices and part to expansion. Whether this expansion will continue now that the allocation of the Exchequer grant is left to their discretion, whether, in particular, local authorities will undertake with enthusiasm the new responsibilities envisaged for them by the Mental Health Bill, cannot yet be known. What will happen is that the conflicting claims of schools and maternity and child welfare services, of community amenities and community care for the disabled, will be fought out in the town hall rather than Whitehall.

So far as the centrally provided branches of the Health Service are concerned, which account for about nine-tenths of its total gross cost, the estimates[1] for 1959–60 show a rise from about £694m. in 1958–9 to £720.6m., a rise which is mainly inflationary—the result of higher prices and wages and salaries—but at least partly expansionary, for, as we mentioned last week, hospital authorities are to have slightly larger capital advances. As has come to be taken for granted, the increase in the cost of running the hospitals dwarfs all the other items. Of the £27m. rise in the total bill, the rise in the revenue advances to hospitals accounts for over £19m. But increases of £2.5m. and £3.2m. respectively are estimated for the pharmaceutical and dental services, and of about £700,000 in the supplementary ophthalmic service. The estimated cost of the general medical services is, however, slightly lower —£74.2m., compared with £74.6m.—even though the estimates have had to take into account the full effect of the 4% interim rise in general practitioners' remuneration, which came into force in January. The findings of the Royal Commission, whatever they may be, cannot, of course, be anticipated in the estimates.

Health Service Expenditure (£m.)

	Actual 1957–8	Final Estimate 1958–9	Estimate 1959–60
Gross expenditure:	**841·4**	**893·9**	**720·6**
Hospitals (capital and revenue)	399·2	431·0	452·8
General medical services ..	70·6	74·6	74·2
Pharmaceutical service ..	71·5	76·6	79·1
Dental service	47·1	50·8	54·0
Ophthalmic service	16·0	15·7	16·4
Other expenditure	37·0	45·2	44·1
Less			
Patients' payments:			
Hospitals	5·2	5·5	6·2
Pharmaceutical	11·8	12·0	12·0
Dental	9·0	11·9	11·9
Ophthalmic	6·2	5·8	5·8
Superannuation and other deductions	34·6	36·6	38·1
Net expenditure	574·6	622·1	646·6
National health contribution ..	63·2	103·1	111·9
Net cost to taxpayer	**511·4**	**519·0**	**534·7**

Who is to pay for this extra £27m. in the gross cost of the centrally financed branches of the Service? The table above (which excludes expenditure on local health services) shows that the patient is not expected to pay any more, except in so far as the charges for pay-beds in hospitals has risen. On the other hand, superannuation contributions will yield a little more because of the rise in salaries and wages. But the bulk of the extra cost is being borne by the insured worker and the taxpayer. The new increase in the Health Service portion of the weekly National Insurance contribution, which came into force last year, will yield an additional £8m. in 1959–60.

[1] *1959-1960 Civil Estimates for the Year Ending 31st March, 1960*, 1959. H.M.S.O., London.

DENTAL CARIES AND PUBERTY

"And so, from hour to hour, we ripe and ripe, And then, from hour to hour, we rot and rot: And thereby hangs a tale"—and also an interesting question: Do the early ripeners rot the soonest? So far as the teeth are concerned, it seems that the answer may be yes. It is known that the time of eruption of the permanent teeth is related to a child's height and weight[1,2]: and from data recorded in the course of an anthropometric survey in Birmingham during 1947 and 1948 it was found that children showing signs of puberty tend to have earlier eruption of permanent teeth than children of the same age who are pre-pubertal.[3] Recently, using findings collected at the examination of 1,730 Edinburgh schoolchildren, J. N. Mansbridge[4] has confirmed these observations. He also claims that, when children of the same chronological age and at an equal stage of dental development are compared, the more sexually mature show a higher prevalence of dental caries than the less mature.

The suggestion that sexual development and susceptibility to caries may be related is important and calls for further investigation. Numerical data of the type collected in the Edinburgh inquiry are difficult to analyse and their interpretation is full of pitfalls for the unwary. Although Mansbridge believes he has proved his case for boys, he is not so sure about the girls. The observation is also of immediate interest because the children of to-day are maturing much more rapidly than their parents and grandparents did. The boy of 11 now is as tall and as heavy as the boy of 13 at the end of the nineteenth century, and adult stature is reached four or five years earlier.[5] Associated with this change there has been a notable reduction in the mean age of onset of puberty.[6] This is easier to measure in girls, and the average age at which the menarche occurs has fallen from about 17 in the nineteenth century to a little over 13 at the present time.

It has been suggested that early maturation may hasten senescence and that a shorter childhood may mean a shorter total life span.[7,8] Certainly in mature rats a diet deficient in calories but adequate in other respects retards development and substantially increases expectation of life.[9] But to argue by analogy from laboratory animals to man is dangerous, and it still seems reasonable to suppose that the early ripeners, with the help of dentures, will live as long as the late starters.

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MAXIMUM PERMISSIBLE DIETARY CONTAMINATION AFTER THE ACCIDENTAL RELEASE OF RADIOACTIVE MATERIAL FROM A NUCLEAR REACTOR

REPORT TO THE MEDICAL RESEARCH COUNCIL BY ITS COMMITTEE ON PROTECTION AGAINST IONIZING RADIATIONS*

After the accident to No. 1 pile at Windscale on October 10, 1957,[1] the Atomic Energy Authority asked the Medical Research Council for advice on the maximum intake of certain radioactive isotopes that should be regarded as permissible, under emergency conditions, for members of the general population living in, or deriving food from, an area contaminated owing to an accident to a reactor.

The Council's Committee on Protection against Ionizing Radiations, together with its Subcommittees on Internal and External Radiations, has considered this problem, and concludes that the intake of radioactive materials by ingestion of contaminated food would generally be the limiting source of hazard after any such accident. Intake by inhalation, or radiation from the exterior, would become of importance only in rather special circumstances.

In the following report, therefore, the Committee proposes maximum permissible levels of dietary contamination for the relevant isotopes in the emergency conditions envisaged. In proposing these levels, the Protection Committee has used the fullest information available on the radiation doses that would be delivered to different body tissues and at different ages by the isotopes concerned, and on the ways in which these materials would enter the body. The Committee wishes to stress, however, that knowledge of the metabolism of radioisotopes is continually increasing and that the subject of permissible doses is constantly under review. In several instances where information has been inadequate we have used the more cautious, rather than the more likely, assumption ; and it is probable that some of our recommended levels are lower than may be regarded as permissible when more information becomes available—for example, on the duration of dietary contamination to be expected following a reactor accident.

The main problem relates to the intake in food of a small group of radioactive isotopes which are produced in high yield by fission of reactor fuel, and which in addition become highly concentrated in certain organs of the body. The Committee's recommendations are expressed in terms of the maximum permissible daily intake of each of these isotopes at various ages, having regard to the metabolism of each element and the period during which the contamination of the food supply is likely to continue.

In view of the specialized problems involved in the assessment of hazards from internal irradiation, estimates are given of the absorbed dose or dose-rate of radiation likely to result in the organs concerned from the proposed levels of intake. It is hoped that these calculations will make it easier to review the significance of the present proposals, and to compare them with the recommendations of the International Commission on Radiological Protection (I.C.R.P.).[2]

It must, however, be appreciated that the recommendations of I.C.R.P., which have been taken into full consideration in the present proposals, do not refer to the problem of an emergency exposure of members of the general population. I.C.R.P. has made recommendations on the maximum permissible intake of numerous radioisotopes for those persons occupationally exposed to radiation. The Commission added that "in the case of the prolonged exposure of a large population the maximum permissible levels should be reduced by a factor of ten below those accepted for occupational exposure." This recommendation was clarified in 1956,[3] when it was stated that it did not refer to the entire population but to "persons who might be exposed unknowingly in the neighbourhood of a plant or source of radiation." It was further stated that "under the conditions at present envisaged, the regions in which the 10% level might be reached would contain a very small fraction of the population and, therefore, the average organ doses per individual of the whole population would be very much lower than 10% of the maximum permissible organ doses for occupational exposure." It is clear that the permissible levels should be lower for persons exposed continuously in the neighbourhood of a plant or source of radiation than for those who are exposed occupationally, since the former group may include children and might apply to lifelong exposure rather than during the period of working life. It is likely, moreover, that those occupationally exposed would be under detailed health surveillance and that the amounts of radiation received by each individual would be known. However, the I.C.R.P. recommendations are estimated on the basis of prolonged exposure, and the levels permissible for transient intake may be higher than those recommended by the Commission for continuous intake.

The main effects requiring assessment are the irradiation of the thyroid gland by radioiodine, of the bone and bone marrow by radiostrontium, and of the whole body by radiocaesium. The position is simplified since (*a*) iodine-131 will be the major contributor to thyroid irradiation, other forms of radioiodine being negligible in comparison, and (*b*) strontium-90 will be of greater importance than strontium-89 in the irradiation of bone. The concentration of either iodine-131 or strontium-90 will therefore, in general, determine the suitability of food for consumption. Since fresh milk will be the main source of these isotopes and of radiocaesium, the concentrations in milk will normally provide a valid basis for control measures.

Since radioiodine is concentrated mainly in the thyroid and radiostrontium mainly in bone, these two materials do not to any serious extent cause irradiation of the same tissues. The recommended maximum intakes of them would not, therefore, be altered in the event of mixed contamination, except that when the intake included both strontium-89 and strontium-90 the levels permissible for each of these isotopes should be

*Members of the Committee: Dr. E. E. Pochin (chairman), Sir Ernest Rock Carling (vice-chairman), Professor D. G. Catcheside, Dr. W. M. Court Brown, Sir John Cockcroft, Dr. L. H. Gray, Dr. L. F. Lamerton, Dr. J. F. Loutit, Dr. J. W. McLaren, Dr. A. S. McLean, Dr. W. G. Marley, Professor W. V. Mayneord, Dr. Sybil Horner, Professor J. S. Mitchell, Dr. G. J. Neary, Dr. G. J. Popják, Dr. F. G. Spear, Professor F. W. Spiers, Dr. Katharine Williams, Professor B. W. Windeyer, and Mr. W. Binks (secretary).

reduced proportionately, since both cause irradiation of bone. Radiocaesium, however, causes irradiation of the whole body, and consequently the presence of appreciable caesium-137 contamination would involve a reduction in the permissible intakes of radioiodine and radiostrontium.

Recommendations

The following recommendations are of the maximum permissible daily intakes, attributable to an accident and in the period following it, of the four isotopes which might be of the greatest importance in determining the suitability of food for consumption—namely, iodine-131, strontium-90 and 89, and caesium-137. The values take into account the likely sequence of rise and fall of food contamination, and are expressed as those permissible at the time of maximum contamination soon after the accident. It is estimated, as described below, that these levels of intake, if continued during the likely course of the contamination, would deliver certain doses of radiation to the tissues most heavily irradiated. These total doses are about equal to the *annual* doses regarded as the maximum permissible ones for these tissues by the I.C.R.P. for those occupationally exposed to radiation. Thus the maximum intakes of iodine-131 proposed for various ages correspond to a total thyroid irradiation of 25 rad, as compared with a maximum annual value of 30 rad during occupational exposure; the intakes for strontium-89 and strontium-90 correspond to a total of 15 rad and an annual rate of 1.5 rad per year respectively, at sites of highest concentration in bone, as compared with an occupational rate of 15 rad per year in bone; and the caesium-137 intake gives a total dose of 10 rad to the whole body, which is less than the maximum annual occupational value of 12 rad for whole-body external irradiation, although greater than the average annual value of 5 rad appropriate to a prolonged continuing exposure.

The recommendations are intended to apply to accidental contamination causing significant exposure of numbers of people small compared with one-fiftieth of the whole population of the United Kingdom, and the Committee has taken into consideration that it is possible but unlikely that the same persons might be significantly exposed to a second accidental release of radioactive material. The following account is intended to summarize and illustrate, rather than to give in detail, the information reviewed by the Committee and the recommended precautions in the event of accident.

Radioiodine.—The recommended maximum permissible initial daily intakes for iodine-131 are 60 mμc per day up to age 6 months, rising to 110 mμc per day at age 3 years, 300 mμc per day at age 10 years, and 1,300 mμc per day at ages over 20. These values assume that the amounts of iodine-131 in the food and in the thyroid decrease at a rate no faster than that due to radioactive decay. Irrespective of the rate of decrease, the maximum permissible total intakes of iodine-131 attributable to the accident would be 650 mμc, 1,200 mμc, 3,400 mμc, and 15,000 mμc for the ages given above.

Radiostrontium.—For the strontium isotopes the recommended maximum permissible daily intakes are 2 mμc per day for strontium-90 and 200 mμc per day for strontium-89, at any age. When the intake includes both isotopes the levels of each should be reduced accordingly.

Radiocaesium.—In the case of caesium-137 the recommended maximum permissible daily intakes are 60 mμc per day at birth, rising to 150 mμc per day at age 6 months and 1,150 mμc per day at ages over 20. These values assume that the amounts of caesium-137 in the food and in the body decrease at rates such that the effective half periods are 10 weeks and 20 weeks respectively. The corresponding maximum permissible total intakes are 6 μc, 15 μc, and 115 μc.

Comments on the Recommendations

Iodine-131

The Committee has considered that the maximum intake of radioactive iodine should be such that the mean radiation dose to the thyroid gland would not exceed 25 rad. The recommended intakes will depend upon the thyroid size and iodine uptake from food at different ages. The mass of the gland was taken to be 1.8 g. from birth to 6 months, 3.4 g. at age 3 years, 9.2 g. at age 10 years, and 25 g. in the adult,[4 5] the uptake falling from 50% in childhood to 30% in adult life.[6 7]

For the calculation of emergency levels of the daily intake of iodine-131, fresh milk is regarded as the most important source of the isotope. If pastures are contaminated with iodine-131 and no loss of the isotope occurs from the herbage except by radioactive decay, the iodine-131 content of milk from the cows grazed on these pastures will reach a maximum value about three days after the contamination and, after the first week, fall with the half period of iodine-131. For children fed on liquid milk only, the maximum thyroid irradiation would be likely to occur at an age of about 6 months, since the thyroid size increases very little from birth until this age, whereas the milk intake may increase with body weight until this age. The maximum permissible intake of 60 mμc per day corresponds to a peak iodine-131 concentration in milk of 0.065 μc per litre, assuming a milk intake of 0.9 litre per day at the age of 6 months. This maximum intake would correspond to a total ingestion of 0.65 μc, which, with 50% uptake into the 1.8-g. gland and prolonged retention, would give a total mean dose of 25 rad to the gland. The values proposed at different ages correspond to the same total mean dose.

It may be noted that the limit of 0.065 μc per litre could be raised considerably provided that young children were fed on dried milk, or liquid milk, from uncontaminated sources. An initial concentration of 0.3 μc per litre would permit normal intakes for children over the age of 3 years (assuming a milk intake of 0.3 litre per day at this age).

Radioactive Strontium

The bone-seeking radioactive isotopes will have a very non-uniform distribution in the skeleton unless the intake is over a long period of time. A basic problem in estimating maximum permissible levels for emergency exposure is whether the calculations should be based on mean radiation dose in the skeleton or local dose at sites of maximum concentration. In the absence of a definite answer to this question, the calculations have been made on the assumption that a certain radiation dose or dose-rate is not to be exceeded at any site of isotope concentration in the bone. If future work shows that mean skeletal dose, and not

this local dose, is the significant criterion it will be possible to increase the values of dietary intake that have been proposed.

A second difficulty arises in that one of the strontium isotopes, strontium-90, has a long half-life (28 years) while the other, strontium-89, has a much shorter half-life (53 days). It would not be reasonable to adopt the same criterion for both isotopes. It was considered, therefore, that for the long-lived strontium-90 the maximum permissible value for emergency exposure should be calculated on a basis of the maximum yearly dose-rate at a site of concentration, while for the short-lived strontium-89 the criterion should be the maximum total radiation dose delivered at any such site. The Committee recommended that in the case of strontium-90 the maximum permissible local dose-rate in mineral bone should be 1.5 rad per year and in the case of strontium-89 the maximum permissible local dose should be 15 rad. Both maximum and mean doses to the bone marrow will be substantially less than those to mineral bone.[8]

Level for Strontium-90.—New bone deposited during the growing period in children will be formed from circulating calcium, which will be derived largely from the current dietary intake contaminated with radio-strontium, but partly also from less contaminated calcium released from older bone during remoulding processes. Moreover, it has been shown that, after the ingestion of a diet containing both strontium and calcium, the ratio of strontium to calcium deposited in bone is about one-quarter of that in the diet. This change in the ratio results from differences in the absorption and excretion of the two elements.[9 10]

If the diet contains 2 mμc of strontium-90 associated with a normal calcium intake of 1 g. daily, the strontium-90 concentration at sites of new bone formation will therefore not exceed one-quarter of this dietary ratio, or 0.5 mμc per g. of calcium. The dose rate in bone at this concentration is rather less than 1.5 rad per year.

Level for Strontium-89.—The level of dietary contamination of strontium-89 which will give a total dose not exceeding a given value at any local deposit can be calculated by integrating the dose rate over time, using 53 days as the half-life. The value for the concentration of strontium-89 in bone which will give a total dose not exceeding 15 rad at the site of the deposit is 50 mμc of strontium-89 per gramme of calcium, corresponding to a daily dietary intake of 200 mμc.

Duration of Intake.—The shorter the duration of intake the greater will be the fraction of the skeleton that is spared irradiation and the smaller will be the size of the deposits of contaminated bone. The calculations have assumed that the deposits have dimensions at least comparable to the range of the beta rays emitted, and if the dimensions are less, values of dose and dose-rate may be substantially lower than those calculated above. Therefore, for intakes limited to short periods—for example, weeks—it may well be that the maximum permissible levels of dietary contamination with strontium-90 and strontium-89 could be raised considerably above the values stated. However, more data on certain aspects of the metabolism of calcium and strontium in bone are required before any higher figures can be recommended.

Prolonging the duration of intake (so long as the daily intake of isotope does not increase) will not affect the maximum local dose-rate calculated for strontium-90. In the case of strontium-89 the maximum total dose at any site is also unlikely to be increased by prolonged intake, since the half-life of this isotope is short compared to its turnover time in bone.

Caesium-137

The Committee considered that the maximum intake of radioactive caesium should be such that the mean radiation dose to the whole body would not in the most unfavourable case exceed 10 rad.

Since fresh milk would be the most important source of radiocaesium, young children, because of their high intake relative to their body mass, would be those at greatest risk. From the way in which caesium enters milk it can be assumed that the contamination of milk would decrease rapidly, and a value of 10 weeks has been taken for its half-period. The evidence following the Windscale accident[11] suggests that this would be an upper limit for the half-value period of radiocaesium in milk. In consequence of this and of the value assumed for the half-period in the body, it may prove that the recommended maximum values for the initial daily intake are unduly low and might safely be higher.

The initial daily intakes which would produce a dose of 10 rad to the whole body are 60 mμc at birth, 150 mμc at 6 months, and 1,150 mμc in the adult, using the following assumptions: (1) the mass of the body is taken to be 3.7 kg. at birth, 8.8 kg. at the age of 6 months, and 70 kg. in the adult; (2) uptake is assumed to be 100% in each case; and (3) a value of 20 weeks is taken for the half-period of caesium in the body[12 13] although some evidence suggests that this value may be unduly high. The corresponding total intakes are 6 μc, 15 μc, and 115 μc. The maximum initial concentration in milk for children at birth and aged 6 months is about 150 mμc per litre in either case.

Limitation of the concentration of this particular radioactive material in food supplies to levels permissible for infants and children would mean that adults would receive doses of whole-body radiation which are much smaller than 10 rad.

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Correspondence

Long-term Anticoagulant Therapy

SIR,—The M.R.C. Working Party's report on the clinical effects of so-called "anticoagulants" (*Journal*, March 28, p. 803) will be studied with the most intense interest. In some ways the committee must have our sympathy in their hard task. The late Professor Topley remarked that once a treatment was accepted as orthodox the organization of a controlled clinical trial became almost impossible. The committee deserves our praise in their effort to overcome these difficulties. Nevertheless withdrawal from the trial was frequently determined by the occurrence of severe cardiac infarcts, and we must appreciate sympathetically the desire of the investigators to apply effective "treatment" at that stage. But it is thus clear that the trial could not be of the true "double-blind" variety, as the investigators must have been aware of which patients were on high and low dosage. A slight bias towards a favourable report may thus have influenced the observations. Nevertheless we have a most valuable documentation which will repay the closest review, and the high professional standing and integrity of the committee members will command respect as well as the most detailed interest in the findings. In view of the immense magnitude of the problem and the costly repercussions of the conclusions, we are in duty bound to ask if all the arguments and observations will stand up to critical commentary. If satisfactory replies are forthcoming to any queries that may be raised the report may compel many radical changes of medical attitudes.

As the difference in mortality in the treated and untreated series was too low to satisfy statistical standards, emphasis is laid on the high frequency of recurrent infarction in the control group. While features for recognition of the original infarction are stringently defined, there is no similar statement of criteria for the recognition of recurrences. A definition would be most helpful, for as clinicians we are often perplexed about the possible meaning of relapses of anginal pain in these patients; only too often further electrocardiograms and study of other clinical features are indecisive. If I understand Tables V and VII correctly, in the 45–54 age period there were 30 control patients with recurrent infarcts, of whom 11 died, while in the high dosage group there were only 7 recurrences, of which 6 were fatal. This could mean that a recurrent infarction under treatment is twice as likely to be lethal. The rarity of non-fatal recurrent infarction in the treated group must indeed be a rather unique and exceptional experience. Suzman (personal communication), though most favourably disposed to the use of long-term anticoagulants, found an almost equal incidence of relapses in his very large series of treated and untreated patients, though they were less fatal in the treated. This is the converse of the M.R.C. findings.

In a statistical trial the results should speak for themselves without special pleading. In the discussion, however, it is stated that the patients whose lives are saved by anticoagulants may survive with more serious heart damage than the untreated patients, thus creating a disparity in death rate unfavourable to anticoagulants after a year or so. This argument is indeed strange when we look at Table XI, which seems to indicate that, if anything, the treated patients were in a slightly better state than the untreated. In any case, if further coronary occlusion is really prevented by anticoagulants, heart damage should be less and not more severe.

I am also uncertain of the statistical propriety of separating off the women and the patients over the age of 55 to make the results look better. In any ideally conducted statistical trial separate groups should surely be defined *before* the trial is begun rather than afterwards.

In most therapeutic trials which have vindicated a remedy it is improvement and reduction of mortality in the patients at greatest risk that compel recognition of the achievement. This applied, for example, in malignant hypertension and in tuberculous meningitis. One would therefore feel that the older age group with more severe atheroma and a greater liability to recurrent clotting should have given a more convincing proof of the efficacy of treatment than the younger group whose disease is likely to be less extensive and whose course is thus more variable.

Your leading article (p. 838) says that anticoagulant therapy in the acute stage "reduces the mortality rate by approximately one-half." The actual reduction found by Wright[1] was from 23.4% to 16%, and there are other well-known reports by Honey and Truelove[2] and by Richards[3] indicating very little benefit at the acute stage. The post-mortem evidence in Gilchrist and Tulloch's series[4 5] showed no significant difference between treated and untreated in the incidence of recent clots: similar findings come from the Presbyterian Hospital, New York.[6] The matter therefore is far from settled. However, if anticoagulants will turn the balance even slightly in favour of the patient it is of course our duty to use them, but we should neither exaggerate the benefits we are conferring, nor must the public in general or the patient in particular be led to believe that a miracle is being achieved. Most of our profession will feel disturbed that this therapeutic trial has given us such indecisive reasons for holding on to a difficult, trying, costly, and often, in practice, disappointing prophylactic regime.—I am, etc.,

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Heinz-body Anaemia Due to Dapsone

SIR,—The article by Dr. R. S. Smith and Dr. Suzanne Alexander (*Journal*, March 7, p. 625) on Heinz-body anaemia due to dapsone is an important contribution to the control of patients under treatment for dermatitis herpetiformis. Ever since the beginning of the sulphonamide era it has been observed that patients under treatment with sulphonamides often develop more or less intense cyanosis, the cause of which has been the subject of debate.

Since we started using dapsone in the treatment of dermatitis herpetiformis we have often observed the appearance of cyanosis, the intensity of which seems to be correlated to the dose of the drug. This cyanosis may at times be alarmingly conspicuous, but does not seem to be due to any physiologically harmful changes in the blood, the patient feeling well and being fully fit for work. One of our patients has, however, experienced, in addition to severe cyanosis, attacks of dyspnoea and pain in the chest. His haemoglobin has also occasionally been subnormal. He has therefore been examined very thoroughly. The conclusion has been that haemolysis was taking place.

It is interesting to note that no Heinz bodies could be detected. Only one attempt was made, however, and the negative result may of course be due to faulty

technique. The number of reticulocytes varied considerably from day to day. It was at times very high (110 per 1,000), and all the time above normal (never less than 12 per 1,000). This patient seems to show the same side-effects to sulphapyridine as to dapsone.

Our impression is that most patients under treatment with dapsone ("D.A.D.P.S.," Bayer) show a raised reticulocyte count from time to time. It seems that this is also true of patients receiving sulphapyridine. This could very well be due to a mild haemolysis fully compensated by intensified erythropoiesis. The examination for Heinz bodies will certainly prove to be an important part of the examination of patients receiving long-term treatment with dapsone, and the same may very well hold true for sulphapyridine and also other sulphonamides.—I am, etc.,

Uppsala, Sweden. MARCUS SKOGH.

B.H.C. and Bone Marrow

SIR,—Your annotation entitled "Does B.H.C. Damage the Bone Marrow?" (*Journal*, December 20, p. 1522) makes it clear that there is a need for further investigation, even though in most of the cases discussed there were complicating factors—including the use of chloramphenicol, which has been incriminated by L. P. Garrod.[1]

In a recent study[2,3] conducted mainly in this unit, nine laboratory workers were exposed for periods of up to 824 hours in the course of a year to outputs of up to 0.53 g./1,000 cu. ft./day of a mixture of lindane–D.D.T. produced by thermal vaporization. This was incidental to a study of the effects upon a variety of species of laboratory animals subjected to continuous exposure. The nine persons have all remained in normal health, and blood counts conducted during and since the investigation indicate that the total and differential white cell picture has remained unaffected.—We are, etc.,

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Aortic Systolic Murmurs

SIR,—In your annotation in the *Journal* of March 21 (p. 777) you relate the common aortic systolic murmur of old people to thickening of the cusps of the aortic valves—on the strength of post-mortem evidence. Whilst agreeing that such systolic murmurs are both common and remarkably benign in the elderly, and therefore important to distinguish from aortic stenosis, I find it hard to believe that mere thickening, without adhesion of the cusps, would cause sufficient turbulence to produce a murmur. A more attractive hypothesis, to my mind, of the mechanism likely to be involved is the systolic injection of blood into a dilated aortic arch. Such widening is not readily apparent at necropsy, but can be seen and convincingly demonstrated during life under the *x*-ray screen.

In other words, I am of the opinion that the common aortic systolic murmur, which is so frequently heard in hospital, now that such a large proportion of our patients are old, is due to dynamic aortic dilatation—itself the consequence of degenerative fibrotic change in the wall of the aorta. It is the sudden rush of blood through a near-normal valve into a dilated and systolically dilating aorta which is responsible for the murmur. Somewhat analogous perhaps is the bicycle tyre: if a partly inflated tyre is blown up with a hand-pump a fair imitation of a systolic murmur will be produced and can be verified by listening to the rim of the wheel with a stethoscope, though the manœuvre requires a discreet assistant and a secluded garage to prevent the circulation of embarrassing rumours about the doctor's sanity.

Referring to the original article by Bruns and Van der Hauwaert,[1] I see the authors confess they were, at one stage, "reluctant to accept these minor changes in the base of the aortic valves as the cause of the murmurs." They dismiss the (to my mind) more attractive theory of aortic dilatation on the grounds of post-mortem mensuration, even though they state quite clearly that the ratio of the widest diameter of the ascending aorta to the diameter of the aortic ring increased from 0.94, on the average, to 1.14 after the age of 50. During life, in aortic systole, this ratio would be very considerably enhanced.—I am, etc.,

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Rubella in Pregnancy

SIR,—While, no doubt, all doctors appreciate a decisive opinion from a consultation, I trust none accepts it without further consideration. Dr. G. F. Abercrombie, in the fifth James Mackenzie Lecture,[1] described the difficulty he had in obtaining a firm opinion for the mother who contracted german measles in the fourteenth week of her pregnancy, and now Dr. Julia Bell, in her article on rubella in pregnancy (*Journal*, March 14, p. 686), claims to provide positive guidance to practitioners faced with Dr. Abercrombie's problem, for she writes that "one can state without doubt that rubella in the early weeks of pregnancy is such a menace to the normal development of the foetus that it constitutes a risk one cannot allow to be taken for the unborn child."

Can we accept such positive guidance, and is it warranted by Dr. Bell's "highly selected" material from *retrospective* investigations? Dr. Robert Ward reports[2] that "recent data from *prospective* studies suggest that the chance of a malformed baby resulting from rubella in the first trimester is in the neighbourhood of 10%," which would seem to be in accord with the opinions quoted by Dr. Noel H. Moynihan in his recent letter (*Journal*, February 28, p. 588) on this subject.

If Dr. Ward is correct then it would seem that Dr. Bell's "rules for the guidance of the practitioner" would involve the sacrifice of nine normal foetuses to prevent the birth of one child with an abnormality which might even respond to treatment to enable it to live a relatively normal life. Do you not think, Sir, that this is rather drastic? At least, let us call in another opinion.—I am, etc.,

Mapperley Hospital, Nottingham J. K. M. MCKAY.

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2 *Current Therapy*, 1958, p. 47. W. B. Saunders, Philadelphia.

SIR,—With reference to Dr. Julia Bell's article on rubella in pregnancy (*Journal*, March 14, p. 686) one is tempted to ask the question: For whose sake is the death of the unborn infant mandatory? (*a*) For God's

sake? The name of life's author is not even mentioned. He has never abrogated this dominion over life. Some of us appear to have forgotten the history of Adam. (*b*) For the child's sake? The unfortunate afflicted with congenital heart disease and other defects expects the Art of Medicine, not death. (*c*) For the mother's sake? It is a poor specimen of womanhood who undertakes pregnancy on the absolute, *sine qua non* condition that her child be perfect. (*d*) For the physician's sake? Thank God there are no medical schools which advocate death for those illnesses we cannot prevent or successfully treat as yet.

To me it is a very grave reflection on the integrity of the medical profession in these islands when an article in its leading journal states emphatically and without controversy "one can state without doubt that rubella in the early weeks of pregnancy is such a menace to the normal development of the foetus that it constitutes a risk *one cannot allow to be taken* [italics mine] for the unborn child. Abortion has become the generally recognized treatment."—I am, etc.,

Enniscorthy, Co. Wexford. JAMES G. DEVLIN.

SIR,—I read with interest Dr. Julia Bell's article (*Journal*, March 14, p. 686). In it she advocates termination of pregnancy in all cases in which rubella occurs before 12 weeks. But does the law allow this? I understand that pregnancy can be terminated lawfully only if it endangers the mother's life or is likely to make her a physical or mental wreck, and that the law does not allow termination for possible ill effects on the child.—I am, etc.,

Wotton under Edge, Gloucestershire. W. M. BROWNE.

A Moral Obligation

SIR,—On March 5 there appeared in the Top Newspaper which is said to be read by the Top People an article entitled "Injustice," which gave an account of the scandalous way in which a member of our profession was treated by his employers—a Regional Hospital Board. This particular newspaper is not noted for its kindly feelings towards our profession, and that it should have been moved to write such an article is indicative of the seriousness with which it regarded this particular happening. It is a depressing thought that not only has there been no appropriate comment or supporting letters from any of our Top People in subsequent numbers of the newspaper concerned, or in the medical press, but save for your leading article (*Journal*, March 14, p. 702) the whole thing has gone unnoticed. Is it that our Top People don't care, or is it that there is room somewhere for a course in Topmanship?—I am, etc.,

Newton Abbot, Devon. A. ROBINSON THOMAS.

Student Suicides

SIR,—The article by Sir Alan Rook (*Journal*, March 7, p. 599) and your leading article (p. 633) are to be welcomed for their informed approach to a difficult subject. It is possible to doubt whether student suicides lie at the centre of the mental illness problem—indeed, suicide may in some degree stand a little to one side of the picture. Most mental illness is non-suicidal, and actual suicides, when they occur, often take one by surprise, even if, in retrospect, one can begin to discern some features of the suicidal personality. Insomnia was an unexpected omission from the mental illness story. Whether insomnia is a primary psychological symptom or otherwise, it is capable of creating a serious vicious circle and may precipitate a breakdown.

It would have been interesting to know something of the intelligence of the students afflicted with mental illness or committing suicide. It may well be that the older universities are at their best in dealing with a certain I.Q. group—say 125 to 170—and beyond these limits there are isolated individuals. Those at the lower end may have difficulties of the type caused by failure to keep up with the crowd. At the other end the difficulty is that the very gifted student, as at school, may find himself not catered for at all. Isolation has been regarded as playing an important part in mental illness, and the association of mental illness with certain physical types may merely be an expression of the fact that certain physical attributes may unfit a student for participation in the more social sports. At Cambridge and Oxford sports lie at the centre of much social activity, and inability to participate in them is automatically isolating. An isolated individual is living in a society essentially alien to him.

A method by which such an isolated individual can become reintegrated with the society around him is by discussing his difficulties, and here we are up against the familiar and awkward problem of who shall be the recipient of his confidences. The monastic tradition of the colleges of the older universities may in a serious way interfere with the operation of the normal confessional mechanisms which operate in society at large. "Who shall confess what, and to whom?" is an inscrutable question, but one of the utmost importance to society. Confessional behaviour permits the most deeply felt emotion of the individual to be shared and so be grafted into the general social experience. Without it society tends to become a mere aggregation of individuals.

There is a medical side to this. It is important for a mentally afflicted student not only to be able to trust his medical adviser but also to be assured that his confidences can go no further. The sight of a doctor taking copious notes is not an inspiring one for him, as he may well be aware that the doctor's notes are not sacrosanct and may on occasion be called into a court of law, and are usually written on paper inscribed with the words, "This record is the property of the Ministry of Health." The desire for secrecy in the treatment of mental illness, remarked on in Sir Alan Rook's paper, is a very reasonable one and every effort should be made to make the secrecy absolute. A student will eventually find himself in an occupation where his mind is his most valuable tool. Mental illness in a student has for him the same implication that damage to the hands would have for a manual worker.—I am, etc.,

Lowestoft. N. B. EASTWOOD.

Live Poliomyelitis Vaccine

SIR,—In relation to the article by Dr. Albert B. Sabin and your leading article on oral immunization against poliomyelitis (*Journal*, March 14, pp. 663 and 700), I would like to add that Cox and associates at our Lederle Laboratories have carried on intensive experiments on the attenuation of poliovirus strains for over ten years and that three strains (Sickle-Mahoney SM Type I, MEF_1 Type II, and Fox Type III) have been given orally to a large number of humans: to date more than 500,000 people have been given at least one type, and, of these, 250,000 have completed immunization with all three types. Each type is given at four-week intervals.

A carefully controlled study, which included 148 families (257 children, 285 adults), has been completed

by the Minnesota Board of Health, and other trials are being conducted with careful medical surveillance in Finland, Cuba, Puerto Rico, Uruguay, Colombia, Haiti, Costa Rica, Japan, Mexico, and Nicaragua.

A large field trial in progress in Costa Rica will include 448,000 children under 13 years and in Uruguay 170,000 have completed vaccination with all three types. In two instances, the Cox vaccine was used in the face of an outbreak; in Managua, Nicaragua, 50,000 children under 10 years were given the vaccine during a Type II outbreak, and in the Andes, Colombia, 6,977 during a Type I outbreak. These studies are being conducted under the auspices of the Pan American Sanitary Bureau in co-operation with the Ministries of Health of the countries involved.

The smaller trials in the other countries above include groups of 50 to 500 children and are being conducted generally by the departments of paediatrics of local medical schools. In Finland, for instance, the whole population of the isolated Sottunga Island is being studied by Professor Nils Oker-Blom of the University of Helsinki.

Titrations of pre- and post-immunization blood samples are being completed to demonstrate the immunologic properties of these attenuated poliovirus strains.—I am, etc.,

F. C. OTTATI,
Director, Medical Research,
American Cyanamid Company.

Pearl River, New York.

Spinal Analgesia in Obstetrics

SIR,—I was most interested in Mr. R. T. Sears's series of spinal anaesthetics in obstetrics (*Journal*, March 21, p. 755), but I am sure that he could eliminate the complication of "spinal shock." He says that he performs a "saddle block," but in fact the anaesthetic reaches T 10 or higher.

It is untrue to say that cinchocaine is "fixed" in two or three minutes; it takes at least 15 minutes. By his technique Mr. Sears produces a spinal block to T 10 or 12, then by placing the patient in the lithotomy position, before complete fixation of the anaesthetic, he removes the lumbar curve and produces a high differential block of the autonomic efferents by the rising diluted cinchocaine, which is too weak to produce a somatic motor block at this level. The result is his "spinal shock."

I would strongly recommend Mr. Sears to use a technique for anaesthesia to a level of T 10, and if he wants a more rapid fixation to use 5% lignocaine. There is little point in using sacral ("saddle block") anaesthesia because in the lithotomy position one really requires anaesthesia of the legs, and anyhow one cannot exclude the possible necessity of intrauterine manipulation even in "low forceps." I also feel that, if a 24 S.W.G. needle was used, there would be much less chance of post-operative headache and it would obviate the necessity of giving a local anaesthetic for the lumbar puncture.—I am, etc.,

Wendover, Bucks. OLIVER WALKER.

Common Bile Duct after Cholecystectomy

SIR,—Mr. L. P. Le Quesne, Dr. C. G. Whiteside, and Mr. B. H. Hand (*Journal*, February 7, p. 329) have made an important contribution to the problem of post-cholecystectomy distension of the common bile duct, and their observations confirm our impression that the common bile duct rarely becomes further dilated after this operation. The theory that some post-cholecystectomy symptoms are the result of an increasingly distending duct would, therefore, appear to have no basis in fact.

The question arises as to what is the cause of the dilatation: is it merely the presence or passage of stones, or is co-existing spasm or fibrosis of the sphincter of Oddi a major factor? It would be interesting to know whether those ducts which have residual stones after cholecystectomy tend to dilate further.

The writers raise the possibility of inaccuracy due to the "injection of fluid into the duct during the operative cholangiography." We have made some observations on this problem. By taking pre-operative *x*-rays at varying degrees of hydrostatic pressure in the common bile duct, we have tried to measure the distensibility of the duct. It is our practice to take two skiagrams: one at the pressure where the sphincter of Oddi opens (usually about 10 to 15 cm.) and the other at 40 cm. pressure—a standard taken somewhat at random.[1] The films so produced are directly comparable, as they are both taken at an interval of a few seconds with an over couch tube at a fixed distance. This makes it possible to give an accurate estimate of the distensibility of the duct at varying pressures.

Assessing 39 recent consecutive cases, we found in 13 with an average pressure rise of 21.8 cm. water that there was no increase of diameter of the duct. In the remaining 26 cases with an average pressure change of 28 cm. water there was an average increase of 1.7 mm. The paper suggests that no significance can be attached to apparent alterations in duct size of 2 mm. or less. It would seem, therefore, that inaccuracies are unlikely from this source. From the survey of a large number of these pre-operative cholangiograms, we concur in the view that 10 cm. to 11 cm. should be taken as the upper limit of diameter of a normal duct.—We are, etc.,

W. M. CAPPER.
W. J. GALL.

Bristol.

REFERENCE

1 Hess, W., *Operative Cholangiographie*, 1955. G. Thieme, Stuttgart.

Needle Biopsy of the Liver

SIR,—In your issue of February 21 (p. 494) your annotator stated that a promising approach to the problem of reducing the risks of needle biopsy of the liver lay in reducing to a minimum the time spent with the needle in the liver. Quoting the new method of Dr. G. Menghini, your annotator suggested that hitherto there has been no liver biopsy apparatus available which reduces the intrahepatic phase to a second or less. It is to correct this erroneous impression that we write this letter.

In his article,[1] Dr. Menghini states that the duration of the intrahepatic phase with the Gillman needle is about 4 to 6 *minutes*! The Gillman biopsy apparatus[2] is widely employed in South Africa and elsewhere, and anyone who has used it will know that the intrahepatic phase may be anything from about one second down to a fraction of a second, depending on the speed and skill of the operator. In principle the apparatus consists of a syringe with wide-bore needle attached. The needle is occluded by a loosely fitting stilette attached to the piston. Once the needle tip is through peritoneum, the handle attached to the piston is held steady in the right hand and the barrel (and hence the attached needle) is advanced by a rapid movement of the left hand towards the liver, to the limit of the adjustable depth-guard. This manœuvre advances the needle into the

liver, withdraws the stilette, and applies suction, all in one movement. The syringe is immediately withdrawn, the needle unscrewed, and the undamaged core flushed out of the needle.

The apparatus is cheap to construct and may be used for hundreds of biopsies without any attention beyond keeping the needle sharp. With the usual precautions and using the transabdominal approach, the risks of complications are minimal (two fatalities in over 3,000 biopsies[3]). Professor T. Gillman, of the Faculty of Medicine, University of Natal, Durban, supplies working drawings of the instrument upon request.—We are, etc.,

M. HATHORN.
N. M. LAMONT.

Durban.

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2 Gillman, T., and Gillman, J., *S. Afr. J. med. Sci.*, 1945, **10**, 53.
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Serum Gonadotrophin in Acne

SIR,—I was interested to read Dr. John H. S. Pettit's paper (*Journal*, February 28, p. 557) in which he reports his experiences with serum gonadotrophin in the treatment of acne vulgaris. His conclusion that no benefit results from this form of treatment is supported by a similar controlled trial recently completed in the skin department here.

A random group of 50 acne sufferers (30 female, 20 male) was included in the trial, a note being made of the severity of the condition as judged by the number of comedones, papules, pustules, and cysts present. Half the patients received the serum gonadotrophin and half a placebo preparation from the hospital pharmacist, on the basis of a code known only to him. It was not until the completion of the trial and after assessment that we knew who had received the active preparation. A course of treatment consisted of 50 units twice daily for four weeks, 50 units daily for the next four weeks, and 50 units on alternate days for a final four weeks. Tablets were issued in bottles of 25 and it was explained that full potency could be assured for only two months once the bottles were opened. Patients were instructed to allow the tablets to dissolve slowly in the mouth, were given a calamine and sulphur lotion to apply at night, and were advised to cleanse the affected parts with a detergent application. They were told not to eat chocolate, bacon, pork, and cheese. At the end of three months the skin condition was assessed as "much improved," "slightly improved," "unchanged," or "worse." One patient failed to complete the course of tablets (subsequently known to contain the active preparation), as she considered they were making her neurotic. None of the others reported any side-effects on the treatment.

Result	Serum Gonadotrophin				Inert Tablets			
	Males	Females	Total	%	Males	Females	Total	%
Much improved	4	4	8	33·3	4	5	9	36·0
Slightly improved	3	2	5	20·8	4	4	8	32·0
Unchanged ..	3	7	10	41·7	2	5	7	28·0
Worse	—	1	1	4·2	—	1	1	4·0

The results in these 49 patients indicate that the serum gonadotrophin in this dosage offers no advantage over the inert preparation. These findings are similar to those of Dr. Pettit and do not confirm the results of R. Aron-Brunetière.[1] He, in an uncontrolled trial with 206 patients, reported cure in 54.9% and improvement in 36.4%. Both R. M. B. MacKenna[2] and E. Lipman Cohen,[3] giving two tablets daily for three months, reported great improvement in over 60% of the cases, and it may be that controlled trials using this higher dosage will give better results than ours.

Of the importance of hormonal influences in acne there can be no doubt, but much more knowledge of the endocrine components is required before we can with confidence hope to prescribe such measures to good purpose without disturbance of the patient as a whole. There is not yet any convincing evidence that serum gonadotrophin is very significant in this syndrome.

It is always exciting to have a new therapeutic weapon against such a stubborn complaint as acne, but more evidence will have to be forthcoming before this relatively expensive form of treatment can be recommended as an addition to time-honoured methods.

I wish to thank Professor J. T. Ingram for his encouragement and Roussel Laboratories Ltd., who kindly supplied the serum gonadotrophin ("gonadyl") and dummy tablets.

—I am, etc.,

G. K. HARGREAVES.

Skin Department,
General Infirmary, Leeds.

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Hazards of Meprobamate

SIR,—I was interested in the letter of Dr. B. W. Cromie (*Journal*, January 17, p. 172) on the subject of your annotation entitled "Hazards of Meprobamate." Dr. Cromie quoted from a report published by Haizlip and myself[1] pointing out that we only observed meprobamate withdrawal reactions in patients receiving *more* than the recommended therapeutic dose. In that report we stated that it seemed necessary to repeat this work with lower doses of meprobamate in a controlled study. This has now been completed and is presently in preparation for publication. At this moment it is sufficient for me to say that only minor withdrawal reactions, such as mild insomnia, appeared in patients previously receiving three or six tablets daily of meprobamate. These reactions occurred with such infrequence as not to be statistically significant. We must conclude that when meprobamate is given in the normal therapeutic range (not more than six 400-mg. tablets daily) the hazard of habituation and the unpleasantness of withdrawal reactions are quite remote.

However, I must repeat that habituation to meprobamate has been described by Fullilove and myself,[2] and by others,[3 4] particularly in people with a history of alcoholism or addiction to other drugs. Meprobamate is a useful drug but should be prescribed with circumspection by the physician, who should provide adequate follow-up of patients receiving it.—I am, etc.,

JOHN A. EWING.

School of Medicine,
University, North Carolina.

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Pleuropneumonia-like Organisms in Genital Infections

SIR,—In her letter (*Journal*, February 21, p. 510) Dr. E. Joan Stokes expresses her disappointment about my not mentioning the search for P.P.L.O. antibodies in my article (*Journal*, January 3, p. 19). A study of P.P.L.O. antibodies in man, made simultaneously with the culture studies I described, is reported in a paper by Dr.

Dorothy H. Card[1] entitled "P.P.L.O. of human genital origin. Antibody distribution in humans and serological classification of strains."

Although I agree with Dr. Stokes that the media she mentions are suitable for the cultivation of P.P.L.O. from human sources, nevertheless it was not until we devised the admittedly complex medium I described that we obtained the high proportion of positives and abundant cultures I reported in my survey.—I am, etc.,

E. KLIENEBERGER-NOBEL.

Lister Institute of Preventive Medicine,
London, S.W.1.

REFERENCE

[1] Card, D. H., *Brit. J. ven. Dis.*, in press.

Personal Medical Record Disks

SIR,—It is surprising that Dr. H. J. Parish's interesting contribution (*Journal*, March 7, p. 640) has not, so far, elicited any comment in your columns. The need for accurate and easily available records of preventive inoculations and other items of medical importance is widely felt and there is equally widespread dissatisfaction with the usual record cards, which, if not mislaid when needed most, are often indecipherable.

Authoritative bodies, such as the Society of Medical Officers of Health, the Central Consultants and Specialists Committee, and—dare we hope?—the Ministry itself, will, in due course perhaps, publish their views on the ingenious device described by Dr. Parish. In the meantime it would be interesting to hear the opinions of individual medical officers of health, senior surgeons in charge of large casualty departments, directors of regional blood transfusion centres, and others.—I am, etc.,

T. F. ELIAS-JONES.

Pathology Department,
Barking Hospital, Essex.

Glass Fragments in Food

SIR,—It appears that no reliable information is available on the extent of injuries arising from glass fragments in foods. The subject is of considerable importance because over 4,000m. bottles or jars are made every year in Britain, 11,000m. bottles of milk are delivered, and it is estimated that 40,000m. glass-packaged foods are sold every year. I am writing to invite the help of any consultants or other officials in hospitals or elsewhere who may have records of such injuries.

I should be grateful for the following particulars: (1) Date. (2) Age group. (3) Nature of injury. (4) Description of glass fragment, dimensions, sharpness, etc. (5) Nature of food or beverage. (6) Any other details of technical interest. I am only interested in injuries sufficiently serious to require medical attention.

If sufficient information is received I will gladly send a digest of it to all who contribute information.—I am, etc.,

J. G. DAVIS.

9, Gerrard Street,
London, W.1.

Musical Hazards

SIR,—I was interested in the article on circulatory effects of trumpet playing by Dr. M. Faulkner and Professor E. P. Sharpey-Schafer (*Journal*, March 14, p. 685) and especially pleased by the practical suggestion made in the last sentence (before the summary).

The only hazard I have so far encountered in 'cello playing, apart from a tremor clearly due to fright at public performances, is a tendency to develop cramp in both hands simultaneously. It comes on quite gradually, and by various manœuvres one avoids being incapacitated. I remember being comforted to read in a biography of Pablo Casals that he had suffered on occasions from the same disability.

Now as in string-playing the two hands are performing quite different tasks it seemed to me that there must be some central mechanism for the cramp; and as I have never had it except when playing string quartets in public, and never until I have been playing for 15–30 minutes, I have ascribed it to the tetany of hysterical over-breathing (another manifestation of fright). If I could bring it on by practising or rehearsing in my own room I would be glad to be the subject of some investigations of alveolar carbon dioxide and of the effect of breathing into a paper bag, but at a public performance I feel that even these simple investigations would be liable to divert the attention of the audience from the serious appreciation of great music.—I am, etc.,

ANON.

Medical Ethics

SIR,—Siamese twins are always good news for the papers, although rarely so for the parents. It is possible that the parents may be willing to let news of the twins' treatment and progress be given for publication in the papers (although one wonders what pressures may have been used), but surely it is contravening medical ethics to publish the names of the doctors concerned, as happened just recently. And if names are published, let the consultants be generous, so that we do not again read that the operation was "performed by Mr. X and his assistant." The only comfort in this miserable affair is the knowledge that the standard of treatment at Bart's is considerably higher than that of its morals.—I am, etc.,

T. C. DANN.

London, N.W.4.

*** In 1955 a conference of representatives of the medical profession and the Press, held under the auspices of the Public Relations Committee of the B.M.A., issued a joint memorandum on the release of news about hospital patients (*Supplement*, October 29, 1955, p. 100). The conference's recommendations were later approved by the Minister of Health (*Supplement*, July 7, 1956, p. 2). "To sum up," stated the memorandum, "a patient's illness ought to be the patient's own personal secret where he wishes secrecy and where secrecy can be maintained. In no way is the secret the personal 'property' (as it were) of his medical attendants, of the nurses, or of the hospital authorities."—ED., *B.M.J.*

POINTS FROM LETTERS

Premenstrual Tension

Dr. ROBERT HEILIG (Jaipur, India) writes: In connexion with the interesting report of Dr. Katharina Dalton (*Journal*, January 17, p. 148), it may be recalled that years ago we found during the first two days of menstruation the permeability for fluorescein of the blood–C.N.S. barrier considerably increased, as compared with the interval figures (R. Heilig and H. Hoff, *Klin. Wschr.*, 1924, **3**, 2049). We explained the frequently occurring premenstrual and menstrual emotional dysbalance with an impaired protective function of the "barrière hématoencéphalique." A few months earlier (*Klin. Wschr.*, 1924, **3**, 1117) I had observed premenstrual water and sodium chloride retention as a physiological occurrence, since recognized as a contributory factor of premenstrual tension.

Obituary

Sir ROBERT MUIR, M.D., Sc.D., LL.D., D.C.L.

F.R.C.P., F.R.C.P.Ed., F.R.F.P.S., F.R.S.

The news of the death on March 30 of Sir Robert Muir, for 37 years professor of pathology at Glasgow University, will be received with widely felt sorrow, especially by Muir's pupils in all parts of the world. He was not the first holder of the Glasgow chair, for he followed a distinguished man, Joseph Coats, who in four years had laid the foundations. But Muir by his work and personality raised the Glasgow school to a position of eminence and indeed made the Glasgow school foremost in the world of pathology. He himself made noteworthy contributions to pathological knowledge, particularly by his studies on immunity and on the metabolism of haemoglobin and bile pigments. His efforts helped to procure the due recognition and independence of the study of pathology, and its appropriate place in the medical curriculum was made secure. His textbooks at once became deservedly popular and are still the grammar of the student of pathology. But his greatest work was done as a teacher, not only of undergraduates but especially of the men who worked under his direction in his laboratory, for they subsequently carried the influence of the Glasgow school far and wide. When on his seventieth birthday in 1934 a *Festschrift*—a special number of the *Journal of Pathology and Bacteriology*—was published in his honour consisting entirely of papers by his former students, there were found to be among the 20 contributors 11 professors of pathology or bacteriology. The quingentenary of the University of Glasgow in 1951 saw the number of his pupils and staff who had attained to chairs of pathology or bacteriology reach the astonishing total of 21, a record which has never been approached in this country.

As a teacher Muir excelled in far more than the technique of teaching. Every teacher worthy of the name has personality, and Muir had it in full measure. Not only had he the necessary basis of knowledge and the scientific vision to make that knowledge live, but he had also sympathy, generosity, and an infective zest for new adventure. He fulfilled Bernard Shaw's definition of the good teacher—"only a fellow traveller of whom you ask the way, and who points ahead—ahead of himself as well as of you." On one occasion Muir said that the atmosphere of adventure was one of the great attractions of pathology: every morning it held out the possibility of something which had not been done or observed before. He revelled in the absence of authority, in the fact that there was no tradition to inhibit the pathologist; he detested anything that savoured of cant or humbug, and a love of truth and fair dealing characterized all he did. Although he worked for the independent status of pathology as a scientific discipline, yet he was proud of the close integration of pathology with the work of the physician and surgeon, and said that the pathologist shared with the clinician the feeling that he was assisting in the relief and prevention of suffering. No wonder that with such a teacher Glasgow became a centre of pathological thought and instruction second to none in the world, and that his pupils "loved the doctrine for the teacher's sake." Indeed, one of the most remarkable features about Robert Muir was his capacity to inspire affection in others. In his earlier years his somewhat reserved and quizzical manner concealed his intense friendliness towards and his keen interest in those who gained his liking. With the passing of the years, however, he shed much of his reserve to younger men, and those who had worked under him in his first decade in the chair were astonished at the friendliness and easy familiarity with which he treated his staff of the last decade. Outside the department, too, and in his retirement he seemed quickly to inspire affectionate regard; perhaps his remarkable gift for being interested in the doings of his friends and remembering to ask about them contributed to this in no small measure. His impatience with formality and pretentiousness in any form increased in his later years, and with it the respectful admiration of his associates.

Robert Muir was born in the village of Balfron, Stirlingshire, on July 5, 1864. Only a few weeks later his father became minister of Allars (United Free) Church, Hawick, one of the Border burghs, and Robert got his schooling at the Hawick Academy. In 1880 he entered the University of Edinburgh, graduating M.A. in 1884. Four years later he graduated M.B., C.M., with first-class honours. Thereafter he was awarded one of the Vans Dunlop scholarships, requiring him to engage in approved research, and this he did in the department of pathology under Professor Greenfield. Two years later he proceeded to the M.D. with a thesis on the reactions of the leucocytes in disease which gained honours and a gold medal. In 1892 he was appointed senior assistant to the professor of pathology at Edinburgh and pathologist to the Royal Infirmary. In 1894 he became a Member and in the following year a Fellow of the Royal College of Physicians of Edinburgh. A few years later when a new lectureship on pathological bacteriology was instituted at Edinburgh Muir was the obvious choice for the initial appointment. In 1898 he was appointed first professor of pathology at St. Andrews on the foundation of the chair. For a year he conducted classes in Dundee, and then came the call to the chair at Glasgow. There he remained until 1936, when he was made professor emeritus and was succeeded by his former pupil John Shaw Dunn. Muir's main work was carried out in the pathological institute of the Western Infirmary, to which he was pathologist, and the whole material of that hospital was available for teaching and research. He became a Fellow of the Royal Faculty of Physicians and Surgeons in 1901.

In 1897 Muir first published jointly with James Ritchie, then in Oxford, the *Manual of Bacteriology*, which quickly became a standard work, reaching its eleventh edition in 1949. Muir's *Textbook of Pathology*, first published in 1924, reached in 1941 its fifth edition, the last from his own pen. He also wrote many scientific papers, and in his later years concerned himself chiefly with the problem of the nature of malignancy as exemplified in the breast. In his earlier years in the Glasgow chair Muir and his collaborators carried out a brilliant series of studies on various aspects of immunity; some of these were collected into a volume, entitled *Studies on Immunity*, which is a classic of its kind. Later this led him to study the effects of haemolytic agents *in vivo*, both chemicals and immune sera; from this developed the work with Dunn on iron storage and utilization, with McNee on haemolysis and jaundice, and with Cappell on intra-vitam staining of the reticulo-endothelial system. Looking back over Muir's life's work one can trace the connecting thread linking each research with his previous work and linking the work of his pupils with his own.

A knighthood was conferred upon him in 1934, and he received many indications of the esteem in which he was

held by the world of learning and medicine. He received the honorary degree of D.C.L. from the University of Durham, of D.Sc. from the Universities of Bristol and of Leeds in 1934, and the LL.D. from the University of Glasgow in 1937. He became a Fellow of the Royal Society in 1911. In 1926–7 he was a member of its council, and in 1929 he was awarded by the Society a Royal Medal for his contributions to the science of immunology. In 1931 he received the rare distinction of Honorary Fellowship of the Royal Faculty of Physicians and Surgeons. In 1935 he was elected Fellow of the Royal College of Physicians of London under the special by-law, and in 1953 he received the Honorary Fellowship of the Royal College of Physicians of Edinburgh. In 1931 he was presented with his portrait in oils, the work of G. Fiddes Watt, on behalf of a number of subscribers headed by the then president of the Royal Society, and on the same occasion a bust by G. H. Paulin was given to the university, which handed it over to the Western Infirmary, where it has ever since occupied an honoured place within the Institute. The Royal College of Surgeons of England awarded him in 1936 the Lister medal—he was the fifth holder of the award and the first recipient who was not himself a surgeon. On the same occasion he delivered the Lister memorial lecture, taking as his subject "Malignancy," with illustrations from the pathology of the mamma.

Muir became a member of the British Medical Association in 1890. He was honorary secretary of the Section of Pathology in 1898, vice-president in 1900, and president of the same or corresponding sections in 1907, 1922, 1930, and at the Centenary Meeting in 1932. From 1928 to 1932 he was a member of the Medical Research Council, and among many other public services may be mentioned membership of the advisory committees of the British Empire Cancer Campaign and of the Imperial Cancer Research Fund, chairmanship of the Foot and Mouth Disease Committee of the Department of Agriculture, and of the Scientific Advisory Committee of the Department of Health for Scotland.

The contributions made by Robert Muir to pathological research in this country cannot be assessed in a memorial notice, but this much can be said, that it is principally owing to him that we have a worthy counterpart in this country of the schools of Ehrlich and Bordet, which, at the time that Muir was carrying out his pioneer work in the study of immunity reactions and mechanisms, were also helping to lay the foundations of the science of immunology. The words of the late Lord Rutherford may be quoted: "During the first decade of this century there emanated from that school"—the school founded by Robert Muir in Glasgow—"a most important series of contributions devoted to the elucidation of the interactions between complements and immune bodies on the one hand and antigen on the other. Haemolytic systems were chiefly studied and problems concerned with the specificity, constitution, and dissociation of immune bodies and with the combining properties of complements were attacked by accurate quantitative methods. These studies by Muir and his collaborators were of fundamental importance in the history of the development of the science. They were embodied in his *Studies on Immunity*, published in 1909, which contains a full description of their bearing upon current theory." On the same occasion the president of the Royal Society, as Lord Rutherford then was, bore witness to Muir's important contributions to knowledge in the larger field of general and experimental pathology. "Among these the most widely known are his researches on experimental anaemia produced by the injection of haemolytic serum and on the regenerative changes in the bone marrow in response to infection. In all these and many other directions the work of Muir and his school influenced the advance of pathology, and although doubtless many further important advances will be made, the work done in the Glasgow laboratories over a period of a third of a century will make an unforgettable chapter in the history of medicine."

Robert Muir was so closely engrossed in what he called the adventure of pathology that he had little time to spare for other interests, but he was an enthusiastic angler, and while on holiday in July, 1955, shortly after his 91st birthday, he hooked and played two salmon on the fly and landed one of them, to his great joy. His memory and intellect remained bright and unimpaired to the end; in the week of his 90th birthday he attended three dinners, at each of which he spoke to the company, and he also made a 20-minute speech without notes on the occasion of a presentation to a former associate and colleague. A month later he flew out to Australia to visit his elder sister, Mrs. Welsh, a trip which he greatly enjoyed. He loved music and the theatre and seldom came to London on official visits without going to one or more concerts or plays.

Robert Muir represented a combination of qualities that is rarely encountered. His passing leaves a gap that cannot be filled: but his inspiration and example will long be remembered by his students and above all by those who had the inestimable privilege of working under him.

Professor D. F. CAPPELL writes: The death of Sir Robert Muir in his 95th year will bring sadness to countless former students, for few men have been so abundantly accorded the respectful admiration and affectionate regard of their pupils. Mention of his activities in the principal's annual letter to graduates invariably brought a shoal of letters expressing delight that he was still going strong, and many of these were from men who had but passed through his class and seen him in the distance during their service in the Western Infirmary.

In private everyone called him "Bobbie," but despite this term of affection he was held in the utmost respect and invariably got the most devoted service from his staff. Such was their regard for him that only the best was good enough to bring to his notice: he himself gave the best—he expected nothing less.

Robert Muir had a somewhat whimsical humour and a great sense of fun, but there was nothing of malice or unkindliness in it. He himself was a man of the utmost integrity and sincerity, and his greatest dislike was of cant and hypocrisy in any form. He was fond of congenial company and delighted in the simple pleasures of good friends, good talk, good food, and good wine. He had great charm of manner and remembered to ask people whom he had not seen for some time about little personal details of home and family, often to their surprise and delight. His many little eccentricities did but endear him further, and many were the stories told of his professorial forgetfulness, of where he had left his car, for instance, or of his disarming replies to some of the acerbities of his colleagues—mostly, according to Sir Robert, apocryphal.

In his younger days he was fond of walking in the hills and of skating, but later golf and angling were his pastimes. He was devoted to both, and the senate golf match with Aberdeen was a never-ending source of pleasure to him. "Bobbie" enjoyed his hobbies so much that he tried, with some success, to convert those of his staff who did not practise them, as he held that some form of outdoor sport was necessary for men working in the laboratory throughout the week. Angling was his greatest love, and fortunately he was able to continue to enjoy it until his 92nd year. His death removes almost the last of the great figures of the Glasgow medical school of the first quarter of this century, and none surpassed him in the fame he brought to the university or in the affection in which he was held by staff and students alike.

F. CHARLOTTE NAISH, M.D.

Dr. Charlotte Naish died at Newcastle General Hospital on March 24, aged 51. During her 12 years of general practice in York she became well known for her infant-welfare work.

Frances Charlotte Naish was born on January 17, 1908, and grew up in Sheffield. She came from a distinguished

Quaker family. Her father, Professor A. E. Naish, was professor of medicine at Sheffield University for many years, and her mother, Dr. Lucy Naish, was lecturer in osteology at the same university. Both now live in retirement. Charlotte Naish was one of eight children, several of whom entered the medical profession. She was educated at Sheffield High School, eventually becoming head girl; at Girton College, Cambridge; and at the Royal Free Hospital, where she won the Owen Roberts scholarship and the Grant medal for surgery. Qualifying in 1933, she graduated M.B., B.Ch. in 1936 and proceeded to the M.D. in 1948. After qualification she was house-surgeon at the Royal Free Hospital, house-physician at the Devon and East Cornwall Hospital, Plymouth, and then returned to the Royal Free Hospital as obstetric assistant, a post she held for a double term, working in hospital and on the district. She had also been a Mabel Webb and A. M. Bird research scholar at her teaching hospital.

In 1935 Charlotte Naish married Mr. Paul Weston Edwards, who was later to give her valuable help, including statistical advice, for her research in general practice. She started her own general practice in Islington in 1936 and also was medical officer at three child-welfare centres. It was here she first formed her conviction that success in infant-welfare work depended on personal contact and continuity, with an all-embracing service to mothers and children given by one individual or group with the right psychological approach. With the outbreak of war her practice and clinics dispersed, and after assistantships in South Wales and Leicestershire she went to York, soon succeeding to the practice of her senior partner.

Through her own observations and clinical acuity she became an expert on breast-feeding, and in 1947 her book on this subject was awarded the Charles Hastings clinical prize of the B.M.A. In 1948 she was able to start what she called her "experiment in family practice," holding a weekly clinic at her surgery for mothers and babies only, and encouraging attendance of all babies in the practice. This original idea of combining preventive and curative medicine is now being adopted by many others. Later a health visitor from the local authority came to help at these sessions.

Charlotte Naish had a keen interest in training students in the organization and scope of good general practice, and medical students from Leeds University attended her clinics during their paediatric course. To encourage preventive medicine and health education in the practice she started a mothers' club, at which talks were given by herself, her partner, and others, and a fathers' club to discuss family problems. Besides her book on breast-feeding she was the author of a number of articles published in this and other medical journals, either alone or in co-operation with paediatricians. Besides these she wrote numerous articles for lay journals on all aspects of infancy and childhood. She also gave lectures to students, nurses, and midwives in training, to many medical gatherings, and took a leading part in many conferences in child health, being twice an invited speaker at Annual Meetings of the B.M.A. She was an excellent speaker, creating a lively interest in her subject.

From 1954 to 1957 she was a member of the first council of the College of General Practitioners and had been re-elected for 1959. While in York she was medical officer to a mother and baby home, a member of the local medical committee, of the city health committee, and of a hospital management committee, chairman of the advisory panel on child health to the Leeds Regional Hospital Board, and a member of Leeds Regional Paediatric Club.

In 1954 Charlotte Naish retired from general practice and started a new venture in Cumberland. With her husband in charge of the educational side, they opened a special school for handicapped children with psychosomatic disorders of various kinds. By limiting numbers she was able to be mother, housekeeper, and resident medical officer to each of the children, and by her understanding and patience brought tremendous improvement and happiness to a number of children whose prognosis seemed hopeless. Her work filled an obvious need, but unfortunately she was too busy there to publish any of her experiences before she died.

Throughout her life Charlotte Naish was a faithful Quaker and frequently spoke at meetings of the Society of Friends. She had many hobbies, with little time in latter years to pursue them. She was second driver and mechanic to Dr. Janet Vaughan when they were the first British women to win the Monte Carlo rally. Next year she herself drove to win the R.A.C. rally. An excellent swimmer, she won the Yorkshire junior championship in her youth. She loved sailing, walking, and the open countryside, particularly the hills of her Cumberland home. One of her favourite relaxations was landscape painting. In addition to a very busy medical life, she was mother to a large family of three daughters and two adopted sons, whom she looked after with untiring energy and often little help. The family were an increasing help to her as they grew older, but none had completed their education when she died.

During the last ten years of her life she had a number of serious illnesses, from each of which she rebounded with the characteristic spirit and courage with which she faced all setbacks. It was hoped that pancreatectomy in March, 1958, would give her many years of good health, but she again went into coma on February 28 last and never regained consciousness.

She will be remembered by many with gratitude for the help she gave them, for her unselfish giving of her energy, but mainly for her love of all children. Our sincere sympathy goes to her husband and all the family in their sad loss.—L. J. L.

P. A. McCALLUM, M.B., Ch.B., D.P.H.

Dr. P. A. McCallum, who had been in practice in Torquay for many years, died suddenly at his home there on March 25, aged 67. He was a Fellow of the British Medical Association.

Peter Alexander McCallum was born on April 22, 1891, and educated at Rothesay Academy and the University of Glasgow, graduating M.B., Ch.B. in 1913. After holding the post of house-surgeon at the Western Infirmary, he became resident physician at the Knightswood and Ruchill fever hospitals in Glasgow. During the first world war he served in the R.A.M.C. in France, being mentioned in dispatches in 1918. On his return to civilian life he was appointed assistant school medical officer to the Glasgow education authority. Soon afterwards, in 1920, he took the D.P.H. of Cambridge and became deputy medical officer of health of Torquay. Later he set up in practice there, specializing in obstetrics.

R. M. S. McC. writes: Dr. Peter McCallum was one of the most respected citizens of Torquay, and his sudden death will be a sad loss. At Glasgow University his was a "vintage" year, producing among others Ian Dingwall Grant, past-chairman of the Representative Body and president of the College of General Practitioners; and he was at school and university with Alexander Hall, a past-president of the B.M.A.

There can be few who practise in the Torquay area who do not owe a deep debt of gratitude to Peter McCallum for his ever-willing help in difficulties: he was one of the old school of obstetric physicians and his skill was remarkable. The services he rendered to the British Medical Association were recognized last year when his name was included in the first roll of Fellows. Before the last war he had been

honorary secretary and twice chairman of the Torquay Division. Every year since the war he had been senior representative at Annual Representative Meetings. A deep and earnest thinker, he never spoke in debates unless he had his facts clearly marshalled, but when he did speak he always held the attention of his audience. He was responsible for the resolution which made the autonomous bodies responsible to the R.B. At these meetings he was always a delightful companion whose knowledge and wit were greatly appreciated by all who worked with him. Torquay Division had been honoured by his agreeing to become general secretary for the Annual Meeting in Torquay in 1960, and, though he had these arrangements already well in hand, his loss at this time is irreplaceable. He leaves a widow and daughter, to whom our deepest sympathies are extended.

Medical Notes in Parliament

MENTAL HEALTH BILL

Before the standing committee on the Mental Health Bill passed from Clause 64 (Power of higher courts to restrict discharge from hospital), Mr. D. RENTON, Under Secretary, Home Office, added on March 24 some further information. It was anticipated, he said, that most people who had been made subject to an order restricting discharge would be sent to State institutions, because they would be convicted people who were generally bad security risks. Some of them, nevertheless, would be considered suitable to go to a hospital instead; it would nearly always be a hospital which had some security arrangements.

Convicted Persons in Hospital

The question arose: how would patients sent to a hospital and subject to special restrictions be treated? The answer was that while they were in hospital one would not know that they were any different from ordinary patients in the same part of the hospital. There would be no segregation; they would be treated as patients. The differences between them and ordinary patients would be those relating to discharge (whether absolute or conditional), leave of absence, and power of recall. Only on these matters would there be a difference. That was perfectly clear, and he hoped would be completely reassuring.

The Home Secretary, when exercising the powers he had with regard to discharge, leave of absence, and recall, would bear in mind not only the security factors but also the medical condition of the patient.

Mr. SOMERVILLE HASTINGS (Barking, Lab.) pointed out that everybody in a hospital ward, particularly when there were cases which remained there some time, would know everything about everybody else. These criminal cases would be marked men from the first. If they must be under control he urged that they should be moved somewhere else, and not kept in a hospital where others had reached a stage at which they could be discharged or have week-end leave.

Mr. RENTON reminded him that even in present circumstances there were a good many people who had made their way from the criminal courts to ordinary mental hospitals. Some were Broadmoor patients and some were transferred prisoners. His understanding was that there had been no trouble or embarrassment experienced by those patients on being sent to ordinary mental hospitals.

The clause was eventually carried by 24 votes to 5.

Progress Reports

On Clause 65 (Powers of Secretary of State in respect of patients subject to restriction orders), Dr. EDITH SUMMERSKILL (Warrington, Lab.) moved an amendment to subsection (6) providing that a periodic progress report should be submitted to the Secretary of State. She said the B.M.A. had not made many pronouncements on this Bill, but it had shown apprehension concerning this category of patients. It had also been said that they must be vigilant to differentiate carefully between treatment and punishment. It would meet the apprehensions of many people if the condition of the patient, with his progress or lack of it, were drawn to the attention of the Secretary of State frequently.

Mr. RENTON expressed a ready sympathy with the spirit of the amendment, that there must be machinery for ensuring that these cases were reviewed from time to time and submitted to the Secretary of State whenever the doctors felt there was a case for discharge. It had so far been intended by the Minister of Health that that purpose should be achieved administratively, in effect by applying the provisions of Clause 43 with regard to periodic renewals. The Minister intended to arrange that the cases of these patients would be reviewed by the responsible medical officer at the same intervals as those for which authority for detention would be reviewed if there were no restriction on discharge, at the end of the first, second, fourth, and seventh years, and thereafter after three years. He could give an undertaking that that would be done. Before the next stage of the Bill the Minister would consider whether something should be written into the clause to ensure periodic reviews, instead of it being left merely to administrative arrangements.

The amendment was accordingly withdrawn, and the clause agreed to. The remaining clauses in Part V called for little comment, and with some minor amendments were approved.

Medico-Legal

CARBON MONOXIDE DEATHS IN PORTUGAL

A MISTAKE RECTIFIED

[FROM A SPECIAL CORRESPONDENT]

The coroner for Southwark, London, Mr. R. I. Milne, has recently held an inquest on the deaths of two persons, English subjects abroad on holiday, who died in Portugal. It did not appear, the coroner said, that their deaths had been adequately investigated, and he quoted *Jervis* for authority to hold an inquiry, the bodies having by this time been brought back to London for further investigation in the mortuary of a teaching hospital which lay within his jurisdiction.

Arthur Trist, 36, a dental surgeon, his wife Patricia, 34, and their two children, aged 2 and 4, had arrived at a motel at Val de Gatos, near Lisbon, on the afternoon of February 11, 1959. During the evening the parents had a meal which included *escalope* of veal and local clams—food which was shared without ill effect by others, though not by the children. Later that evening the children were put to bed and both the parents used the bathroom, the husband having a bath (a water level being found later) and the wife washing some stockings (which were later found unfinished). A maid called at 10 o'clock next morning but could obtain no reply; when she failed to obtain a response at 12 noon and again at 4 p.m. she called the manager and the premises were forced open. Both parents were found dead, spread-eagled in curious positions, partly dressed, in rooms adjoining the bathroom. The children, who had occupied another room, were alive.

Alleged Clam Poisoning

Both parents' bodies were examined first by local practitioners, who, finding vomit soiling of the lips and clothing, suspected food-poisoning. This view appeared to colour the whole investigation, for it was the only possibility entertained in spite of the fact that a waiter admitted finishing, without ill effect, what was left of the clams the couple had been eating. The Portuguese authorities continued their investigations into this question, the Tribunal of Almada first issuing a statement that results would not be available for some days, then saying that death was undoubtedly due to clam poisoning, but refusing to provide details to an English press which was by this time

alert to the interests of the case, and finally disposing of the problem by a document which said that the cause of death was "ill defined." By this time medical friends of the Trists and a journalist who had brought the children back to England had discovered that the parents had taken out a standard accident policy for the sum of £10,000 to cover the period of their holiday. Concern was expressed at the procrastination and lack of detailed information about the cause of death, and the advice of a London forensic pathologist, Dr. Keith Simpson, was sought. He agreed to see the premises and examine the bodies in Portugal if permission could be obtained, but this was refused. Nevertheless a doctor friend of the Trists and the journalist who had been in on the case from the start flew to Lisbon and were allowed by the manager to inspect the motel, take photographs, and make measurements of the rooms.

It had seemed quite likely that these two persons who had died so suddenly after using a bathroom had succumbed to inhalation of fumes—from some form of heating, possibly from lack of ventilation, for :

1. The food had been shared, only the Trists dying.
2. The season for clam (plankton-alkaloid) poisoning had not yet arrived.
3. Death had been so very rapid, as indicated by the sprawled bodies.
4. Vomiting is a common terminal event in fume-poisoning—and commonly causes suspicion of food-poisoning.
5. Both victims had used the bathroom almost immediately before their deaths.
6. It had been found on visiting the motel that the bathroom was very small, measuring 8 ft. by 4 ft. 6 in. by 10 ft. 3 in. (2.4 by 1.4 by 3.1 m.), contained a butane continuous-flow water heater *without a flue*, and had most inadequate ventilation: only a few small slits had been set in one half of a closed window.

In view of the difficulty experienced in obtaining authority to see the bodies, they were flown back to England on February 27 and examined in a London teaching hospital mortuary on the following day.

Cherry-pink Stains

It was at once noticed that the livid stains in the skin were distinctly cherry-pink—the characteristic colour of carbon monoxide poisoning. Blood which showed the same tint was examined by Wolff's (qualitative) and the Hartridge spectrometer (quantitative) method and found to contain between 50% and 54% HbCO. Various samples of blood, of muscle, and of bone marrow gave similar figures. This was 16 days after death. (It is not generally recognized that the combination of CO with haemoglobin is a remarkably stable one, both blood and muscle keeping well for many weeks after death.) Both bodies were well preserved by refrigeration, and samples of blood and tissue were in good condition ; the organs had been removed in Portugal and retained.

These findings were obviously of such vital importance from the insurance point of view that the coroner was informed. He agreed to allow the observations (which were denied by the Portuguese authorities) to be checked, and a second Home Office pathologist examined the bodies, made his own analysis of blood and muscle, and confirmed the findings. Samples were also submitted to the Director of the Science Laboratories of New Scotland Yard, who confirmed the readings, and another sample of muscle was sent, sealed, as an "unknown" to the Research Officer in charge of the R.A.F. unit at Farnborough, which has particular experience of analysis of muscle for CO in fire and fire-fume inhalation in aircraft accidents. Specimens from both victims were reported by him as revealing "0.65 ml. CO per 100 g. wet tissue," such quantities of carbon monoxide as had been "found in human muscle only in the presence of blood saturations of approximately 60% HbCO or above."

Butane Gas

These findings were reported to the coroner, who decided to hold an inquest on March 6. He heard evidence of the Trists' habits from a doctor friend, and of the circumstances from the journalist who was on the scene at the time. The journalist produced a plan of the motel, measurements of the rooms, and photographs, which included the water level in the bath, the geyser in question, and the sole vent operating in this small room. An English butane gas chemist, who produced a photograph of the "Vaillant Supérieur," gave evidence that it would be dangerous to use it in a small room without a flue. He added that it was of a size designed to supply a sink and not a bath. If the bathroom door was shut and a bath was run or water was used for washing, the ventilation slits would be hardly sufficient to provide the geyser with enough air to enable it to burn, and would result in much CO_2 being re-burned to CO ; a saturation of 0.28% of CO would be reached in about one hour. This is a saturation which normally causes a blood figure of 60% to be established in approximately one hour.

Verdict

The coroner said that the evidence left no doubt about the cause of death and returned a verdict of "accidental death from carbon monoxide poisoning from the inhalation of the products of combustion of butane gas in an inadequately ventilated atmosphere" in each case.

A legal representative of the insurance company then stated that he had been instructed to say that any proper claim would be met.

Although these findings left no room for doubt that CO inhalation was the sole cause of death, it was thought that it would be of interest to examine vomit which soiled the clothing of both parents for the alkaloids of clams, which, later in the season, can cause sudden severe illness and may cause death. Wagner's and Mayer's tests for these water-alcohol (plankton-borne) alkaloids were negative. It will be remembered that the organs had been removed in Portugal. In any case the high CO saturation left no room for doubt about the cause of death.

The case illustrates what is well known in England as a result of the concern felt in recent years over the rising toll of accidental deaths from domestic gas. Both the B.M.A. committee and the Gas Board's figures show that inadequate ventilation, often unrecognized, accounts for 7–8% of these accidental CO deaths. It is not uncommon, when vomiting occurs in the last stages of CO poisoning, to have suspicion of food-poisoning aroused. Many people do not notice the stale smell of gas fumes, and the distinctive cherry-pink colour is commonly overlooked—especially when the possibility is not borne in mind.

Coroner's Jurisdiction

This case illustrates very clearly the rule that a coroner's jurisdiction is not determined by the place of the death. The coroner's ordinary jurisdiction is confined to the area for which he was appointed coroner. Whenever the circumstances require an inquest, the coroner has jurisdiction so long as the body lies within his area. It often happens that a body is moved from one jurisdiction to another—for instance, after a road accident or an air crash. In such case the coroner of the area to which the body is moved will have jurisdiction to hold the inquest. Moreover, if a coroner thinks it expedient he may authorize or order the removal of a body from his area to the area of another coroner for inquest.

A coroner has no power to make, as it were, an extradition order for the conveyance of the body of an Englishman from a foreign country to England. But if the body can be obtained through whatever processes are laid down by the law of the foreign country, or by diplomatic means, the mere presence of that body within an English coroner's area will give him jurisdiction. A body may be removed from England only with leave of the coroner who has jurisdiction over it.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **March 21** (No. 11) and corresponding week 1958.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire
Diphtheria	3	0	1	0	1	1	0	4	0	
Dysentery	1,171	133	136	14		1,187	117	264	9	4
Encephalitis, acute	1	0		0		4	0		0	
Enteric fever:										
Typhoid	0	0	0	0		3	0	0	0	
Paratyphoid	9	2	0	0		2	0	3(B)	0	11 (B)
Food-poisoning	131	9	9	2		144	20	7	0	
Infective enteritis or diarrhoea under 2 years				14	18				6	26
Measles*	22,338	1262	1136	510	666	4,007	140	92	29	12
Meningococcal infection	30	3	6	2		29	2	8	1	1
Ophthalmia neonatorum	29	8	0	0		34	2	6	0	
Pneumonia†	1,452	58	369	15	13	537	32	261	20	11
Poliomyelitis, acute:										
Paralytic	8	2	1	0		13	1	3	1	7
Non-paralytic	3	1	0			5	1			
Puerperal fever§	197	33	7	3		207	33	14	1	
Scarlet fever	1,084	53	66	22	13	910	64	88	35	39
Tuberculosis:										
Respiratory	647	58	95	14		586	47	119	22	
Non-respiratory	59	4	9	1		74	6	10	2	
Whooping-cough	533	17	55	42	125	555	25	32	8	14

DEATHS	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	0	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	2	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	5	0	0	0		7	0	1	0	1
Influenza	590	16	17	3	17	79	3	4	0	1
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	0	0	0		0	0		
Pneumonia	1,058	75	40	36	16	693	64	37	16	12
Poliomyelitis, acute	2	0		0	0	0	0		0	0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	102	13	10	0	3	98	6	13	2	4
Non-respiratory		1	1	0	1		1	0	0	1
Whooping-cough	0	0	0	0	0	0	0	0	0	0
Deaths 0–1 year	319	38	42	7	13	343	32	26	7	19
Deaths (excluding stillbirths)	11,985	868	753	167	228	11,462	896	666	138	192
LIVE BIRTHS	15,766	1341	1120	257	322	15,468	1280	961	240	364
STILLBIRTHS	322	26	27			319	19	31		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

Week Ending March 28

Infectious Diseases

Areas where numbers of notifications were high in the latest two weeks for which figures are available.

	Week Ending Mar. 21	Week Ending Mar. 28
Measles		
Berkshire	299	**371**
Easthampstead R.D.	90	**172**
Devonshire	189	**232**
Plymouth C.B.	70	**123**
Durham	1,003	**1,009**
Sunderland C.B.	216	**145**
West Hartlepool C.B.	73	**172**
London	1,262	**1,360**
Lambeth	96	**182**
Lewisham	116	**146**
Wandsworth	152	**145**
Staffordshire	876	**936**
Stoke-on-Trent C.B.	163	**200**
Surrey	1,691	**1,354**
Croydon C.B.	159	**214**
Surbiton M.B.	160	**101**
Sutton and Cheam M.B.	160	**100**
Yorkshire West Riding	2,426	**2,122**
Bradford C.B.	269	**162**
Huddersfield C.B.	112	**118**
Leeds C.B.	446	**507**
Sheffield C.B.	379	**300**
Dysentery		
London	133	**137**
Greenwich	15	**20**
Islington	10	**18**
Southwark	16	**33**
Lancashire	88	**129**
Blackburn C.B.	13	**33**
Surrey	58	**91**
Coulsdon and Purley U.D.	—	**41**
Croydon C.B.	29	**9**
Acute Poliomyelitis		
London	**3**	**3**
Hampshire	**2**	**3**
Lancashire	**0**	**3**

Outbreaks of Paratyphoid Fever

Within the last two weeks outbreaks of paratyphoid fever have been reported from mid-Sussex, the Medway towns of Rochester, Chatham, and Gillingham, and the metropolitan borough of Southwark.

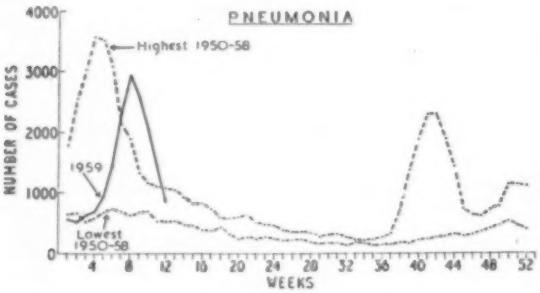
The outbreak in mid-Sussex began on March 20 when two children from Crawley who had been admitted to Queen Mary's Hospital, Carshalton, for investigation were found to be suffering from paratyphoid B infection. By March 25 five further cases had been admitted. It was at first impossible to trace any common factor, but a report from Chatham on March 26 of a small outbreak in the area of the Medway Towns suggested the possibility of some association, particularly since the strain of organism in both districts belonged to phage type 3a. By April 1 a total of 12 cases from Crawley had been confirmed, the ages ranging from 3 to 16 years. Two children presented with the symptoms of acute appendicitis, one of whom was found at operation to have an acutely inflamed appendix. Two had meningeal signs when first seen, suggesting the possibility of non-paralytic poliomyelitis, while one showed respiratory symptoms with fever and presented a picture of basal pneumonia. Five children developed typical rose spots when in hospital. It is probable that infection was conveyed

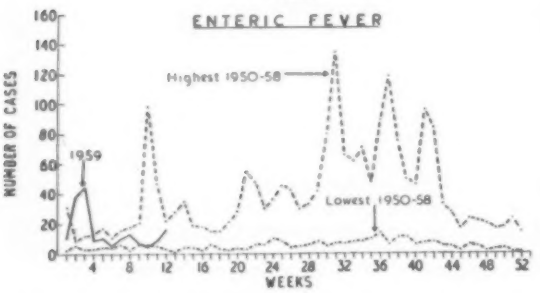
through confectionery, although so far bacteriological proof is lacking. If this view is correct it is unlikely that any further primary cases will occur. However, routine sampling from family contacts showed that four parents were carrying the organism, so secondary cases may yet come to light.

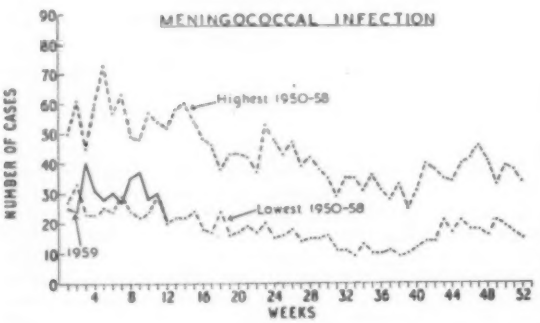
Fourteen cases of paratyphoid B infection have occurred in the Medway area of Kent, and in Southwark there are 7 confirmed cases, the majority of which reside in one ward of the borough. Investigations into the cause of these outbreaks continue.

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1950–8 are shown thus ------, the figures for 1959 thus ———. Except for the curves showing notifications in 1959, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.







Scotland's Health

The Report of the Department of Health for Scotland for the year 1958 records the lowest infant mortality rate so far achieved—27.7 per 1,000 live births. But the figures for Clydeside are higher than those for the rest of Scotland, the rate for Glasgow being 35. Men over 45 are the only section of the Scottish population with a rising death rate: this is "almost wholly attributable to cancer of the lung and to heart disease, mainly coronary thrombosis." There are about 25,000 new cases of cancer each year in Scotland. Between the ages of 50 and 65 there were 8,078 male deaths from all causes: of these 2,008 deaths were from all forms of cancer and 924, or 46% of the cancer deaths and 11% of all deaths at these ages, were due to cancer of the lung and bronchus. In Scotland the incidence and death rate of chronic bronchitis are high, "about the highest anywhere."

So far as town and country planning is concerned, the report states that the most significant single factor in Scotland continues to be the need for dispersal of population and industry from Glasgow.

Medical News

Clean Food in Scotland.—The new Food Hygiene (Scotland) Regulations, 1959, contain provisions for securing the hygienic handling of food and drink by anyone whose person or clothing is likely to come into contact with food in the course of conducting a food business; and for regulating the construction and cleanliness of equipment and premises. The provisions covering personal hygiene become effective on May 1, while others, mainly those relating to the construction of premises, will be in force from October 1.

New B.S.I. Safety Standards.—The British Standards Institution, recognizing, as they say, that children "like to take it out on the cot," have recently published two specifications for safer cots which will help to cut down accidents due to children getting jammed in the bars, toppling over the sides, or consuming toxic paint or other substances. Another standard, published on April 9, defines what should be expected of a textile which is claimed to be flame-resistant. The durability of flame-resistance can be seriously affected by washing, and the standard therefore lays down that to earn a low flammability label sample fabrics must survive a stringent washing test. The even more exacting demands of flame-proof industrial clothing are met by further new specifications. Government regulations enforcing these new specifications for clothing will come into effect on May 11.

W.M.A.—At the thirty-fifth Council Session of the World Medical Association held in Sydney, Australia, from March 25 to April 5, Dr. RENAUD LEMIEUX, professor of medicine at Laval University, Quebec, Canada, was elected President-Elect of the association for the term 1958–9, to fill the vacancy caused by the death of Dr. L. GÉRIN-LAJOIE. Dr. J. M. BISHOP, of Bellevue, Washington, was appointed Deputy Secretary-General of the W.M.A.

Colonial Development Schemes.—Grants made under the Colonial Development and Welfare Acts totalled £1,620.000 during the month of February. Of this sum £199,300 was for the construction of a new hospital at Savanna-la-Mar, Jamaica; £87,255 for a new general hospital in Barbados; £21,100 for a science block at the New Gambia High School; and £12,784 to North Borneo for a malaria control project.

Jerusalem Ophthalmic Hospital.—Sir STEWART DUKE-ELDER, the Hospitaller of the Order of St. John, gave an illustrated lecture at St. John's Gate, Clerkenwell, on March 20, on the progress of the new hospital and research centre being built in the Arab part of the city of Jerusalem. The research laboratories of the hospital have been in use for some time, and it is hoped that the hospital itself will be officially opened in the autumn of next year.

Royal Australasian College of Surgeons: Alan Newton Prize.—The College awards a biennial essay prize in memory of the late Sir ALAN NEWTON, a foundation fellow of the College, and later its president. The subject for the 1960 prize is "The Pathology and Surgery of Hernias of the Abdominal Wall," and the closing date is December 1, 1960. Details from the Secretary of the College, Spring Street, Melbourne, C.1, Australia.

Hunterian Society's Gold Medal Essay Competition.—The subject for the 1959 essay is "The Use and Abuse of Sedatives." The competition is open to all general practitioners resident within the British Commonwealth. Further details may be obtained from the honorary secretary, Mr. GEORGE QVIST, 72, Harley Street, London, W.1.

Penicillin Agreements.—Beecham Group Ltd. signed agreements with Bristol Laboratories Inc., of Syracuse, New York, on April 2, in New York, which will bring substantial dollar royalties to this country in the event of new products derived from the recent Beecham penicillin discovery being marketed in the United States.

Dr. C. F. Harris, physician in charge of the Children's Department, St. Bartholomew's Hospital, has been re-elected vice-chancellor of London University from September 1 for the university year 1959–60.

Dr. W. W. Kay has been appointed Vice-moderator, and in due course Moderator for 1960 to 1961, of the Free Church Federal Council. He is senior pathologist at the Mental Hospital Group Laboratory at West Park Hospital, Epsom.

London Hospital Medical College.—Mr. G. L. SLACK has been appointed to the chair of dental surgery tenable at the College from May 1.

Professor J. N. Davidson, Gardiner Professor of Physiological Chemistry at the University of Glasgow, is visiting Poland at the request of the biochemical committee of the Polish Academy of Sciences. He will lecture at the universities of Warsaw and Cracow.

Professor Muhiddin Erel, rector of Ege University and director of the Institute of Hygiene and the Institute of Microbiology, Izmir, Turkey, is now in London at the invitation of the British Council. He will study medical and university education and the training of British nurses.

Mr. A. Dickson Wright was given a dinner on March 21 by all the housemen and registrars who had served under him at St. Mary's Hospital.

COMING EVENTS

St. George's Hospital Medical School.—Owing to rebuilding it will not be possible to hold the usual postgraduate demonstrations in psychiatry and neurology on Thursdays at 5 p.m. during the Summer Term beginning April 13. They will be resumed in October, 1959.

First Almroth Wright Lecture.—"Antigens of Pathogens," by Dr. D. A. L. DAVIES. For details see advertisement in this week's *Journal* (p. III of cover).

Occupational Aspects of Ageing.—This one-day conference on current research will be held on April 21 at the Industrial Welfare Society, Robert Hyde House, 48, Bryanston Square, London, W.1. Fee for the conference is £2 12s. 6d. (or £3 3s. for delegates from organizations not in membership with the I.W.S.). Details from the Society, at the above address (AMB 2401–6).

International Seminar on Health Education.—The Central Council for Health Education will hold an international seminar in London from April 21 to 24 at the London School of Hygiene and Tropical Medicine, Keppel Street, London, W.C.1. Further details from the Council, Tavistock House North, Tavistock Square, London, W.C.1.

Manchester Medical Exhibition.—This exhibition is to be held at the City Hall, Manchester, from April 27 to May 1 and will be officially opened by Professor Sir GEOFFREY JEFFERSON. Further details from organizers, British and Colonial Druggist, Ltd., 194–200, Bishopsgate, London, E.C.2.

British Orthopaedic Association.—Spring meeting with the French and Belgian Orthopaedic Societies at Torquay and Exeter from April 30 to May 2. Further details from the British Orthopaedic Association, 47, Lincoln's Inn Fields, London, W.C.2.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, April 13

●ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5.15 p.m., Mr. R. L. Holt: Trends in the Surgical Treatment of Peptic Ulcer; 6.30 p.m., Professor C. G. Rob: Place of Surgery in the Treatment of Arterial Hypertension.
ROYAL COLLEGE OF SURGEONS OF EDINBURGH.—5 p.m., Professor J. H. Louw (Capetown): Intestinal Malrotation and Duodenal Ileus.

Tuesday, April 14

BIRMINGHAM MEDICAL INSTITUTE.—8 p.m., symposium: Local Psychiatric Research. Papers by Dr. H. C. White, Dr. L. Zollman, and Dr. H. Halstead, Ph.D.
MANCHESTER MEDICAL SOCIETY: SECTION OF SURGERY.—At Royal Manchester Children's Hospital, Pendlebury, 4 for 4.30 p.m., clinical meeting.
ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Lumleian Lecture by Dr. Edward J. Wayne: Clinical and Metabolic Studies in Thyroid Disease.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Arris and Gale Lecture by Mr. G. L. Bourne: Anatomy, Physiology, and Pathology of the Human Amnion and Chorionic Membranes.
●ROYAL COLLEGE OF SURGEONS OF ENGLAND.—6.15 p.m., Mr. Harold Dodd: Concept of Varicose Veins and their Allied Conditions.
ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Theatre, 5 p.m., Mr. Lionel Higgins: Abruptio Placentae (Accidental Haemorrhage).
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Dr. G. F. Swann: Encephalography or Ventriculography?

Wednesday, April 15

HARVEIAN SOCIETY OF LONDON.—8.15 p.m., Dr. Stephen J. Hadfield (Assistant Secretary, B.M.A.) and Dr. Alistair French: Medical Ethics.
NORTH-WESTERN THORACIC SOCIETY.—At Aintree Hospital, Liverpool, 5 p.m., Dr. Brian Taylor: Masters, Methods, and Memories.
ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH.—5 p.m., George Alexander Gibson Lecture by Mr. T. Holmes Sellors: Contribution of Surgery to Clinical Cardiology.
●ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5.15 p.m., Dr. M. Bodian: Fibrocystic Disease of the Pancreas; 6.30 p.m., Mr. D. Innes Williams: Congenital Abnormalities of the Upper Urinary Tract.
ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—3.30 p.m., Dame Anne Bryans: Work of the British Red Cross Society Throughout the World (illustrated).
WEST LONDON MEDICO-CHIRURGICAL SOCIETY.—At Royal Society of Arts, 8.30 p.m., Cavendish Lecture by Sir Wilson Jameson: Laying the Foundations.

Thursday, April 16

BRITISH INSTITUTE OF RADIOLOGY.—8 p.m., Silvanus Thompson Memorial Lecture by Professor G. Stead, D.Sc.: 1895 and All That.
HYPNOTHERAPY GROUP.—At Royal Society of Medicine, 8 p.m., Dr. J. A. Hadfield: Clinical Importance of Infantile Experiences.
MANCHESTER MEDICAL SOCIETY: SECTION OF ANAESTHETICS.—At Liverpool Medical Institution, 8 p.m., joint meeting with members of Liverpool Society of Anaesthetists. Dr. I. C. Geddes: Hyperventilation in Anaesthesia; Dr. A. R. Hunter: Some Experimental and Clinical Observations on Analgesic Drugs.
ROYAL ANTHROPOLOGICAL INSTITUTE.—5.30 p.m., Dr. G. Ainsworth Harrison: Environmental Determination of Mammalian Morphology (illustrated by slides).
ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Lumleian Lecture by Dr. Edward J. Wayne: Clinical and Metabolic Studies in Thyroid Disease.
●ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5.15 p.m., Mr. J. Leigh Collis: Tumours of the Oesophagus; 6.30 p.m., Mr. L. S. Walsh: Surgical Treatment of the Cerebral Vascular Accident.
ROYAL EYE HOSPITAL.—5.30 p.m., Dr. T. H. Whittington: Aspects of Refraction Work—(3) Prisms in Refraction Work.

Friday, April 17

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. J. R. Bignall: clinical demonstration.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., clinical discussion for general practitioners by Mr. Anthony Radcliffe: Dysphagia.
KENT AND CANTERBURY HOSPITAL.—8 p.m., clinical meeting.
LEICESTER CHRISTIAN MEDICAL ASSOCIATION.—At Leicester Royal Infirmary, 8.45 p.m., Reverend F. S. Sinker, M.B., B.Ch.: Christian Trends in Present-day Medicine.
●ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5.15 p.m., Dr. J. H. Middlemiss: Radiology in Acute Abdominal Emergencies; 6.30 p.m., Mr. A. L. Eyre-Brook: Tendon Transplantation.
YORKSHIRE THORACIC SOCIETY.—At Instructional Block, General Infirmary at Leeds, 7 p.m., Dr. Paul Wood: Modern Auscultation.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Eustace.—On March 12, 1959, to Dr. Jean Musgrave, wife of Dr. Philip F. Eustace, of 47, Englishcombe Lane, Bath, Som, a daughter—Joanna.
Young.—On April 1, 1959, in Saskatoon, Canada, to Margot, wife of Dr. F. O. Young, a daughter—Janice Nicole.

DEATHS

Clindening.—On March 23, 1959, at 301, Clive Court, Maida Vale, London, W., Frederick Talbot Driffield Clindening, M.R.C.S., L.R.C.P., aged 99.
Couche.—On February 16, 1959, James Buxton Couche, M.D., of San Diego, California, U.S.A., aged 88.
Knapp.—On March 21, 1959, at his home, Gloucester House, Barry Road, Dulwich, London, S.E., William Knapp, M.B., B.Ch.
Martin.—On March 20, 1959, at Hayling Island, Hants, John James Black Martin, M.D., F.R.C.P.Ed., D.P.M., of The Chart House, Swanage, Dorset.
Millar.—On March 25, 1959, William Baldwin Millar, M.B., Ch.B., of 205, Pitshanger Lane, Ealing, London, W.
Morel.—On March 25, 1959, Mervyn Philip Morel, M.B., F.R.C.S., of Beech Hill, Barnstaple, Devon, aged 51.
Pritchard.—On March 21, 1959, Eric Law Pritchard, M.D., of Knowle, Coombe, Sidmouth, Devon, formerly of Hampstead, London, N.W., aged 90.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Aetiology of Diabetic Cataract

Q.—*What is the metabolic cause of cataract in diabetes?*

A.—The term "cataract in diabetes" is somewhat vague, and might be taken to include any form of cataract which may occur in patients suffering from this disease. The following observations apply only to true diabetic cataracts and are based on experimental work carried out for the most part on rats. It is generally agreed that the time required for cataract formation in the diabetic rat is inversely related to the degree of hyperglycaemia. Factors which tend to reduce the level of hyperglycaemia, such as fasting, high fat diet, and the administration of phlorizin, are beneficial in preventing cataracts. Hyperglycaemia must therefore play a role in the production of diabetic cataracts, but not necessarily a direct one. If a lack of insulin produces cataracts, then cataracts may be a result of an inability to obtain energy by utilizing glucose. Since the lens depends on glucose for a major portion of its energy, the total available energy is lowered beyond the critical point that is necessary for maintaining transparency. A decrease in energy could produce cataracts by stopping the synthesis of glutathione, enzymes, proteins, or other structural compounds, or by blocking the maintenance of a water and electrolyte balance. This hypothesis, put forward by Patterson,[1] is supported by studies on glucose uptake on isolated lenses and by studies with diets that supply energy-yielding substances other than glucose.

REFERENCE

1 Patterson, J. W., *Diabetes*, 1956, 5, 93.

Alcohol in Moderation

Q.—*What are the modern views about the harmfulness or otherwise of alcohol in moderation—for example, a couple of glasses of wine such as sherry and perhaps a cocktail or two, daily?*

A.—The long-term effect of small amounts of alcohol in the form of sherry or cocktails may be said to depend on habits, on age, and on constitution. There are, of course, no scientifically established findings. The effect of alcohol on body organs must depend on the rate at which it is destroyed, and this will be the more rapid when metabolism is vigorous. A vigorous metabolism is promoted by exercise, and it is reasonable to suggest that the harmful effect of alcohol will be less in those who take regular exercise. The man who rode regularly to hounds could take his port without undue hazard to his health.

Similarly it is reasonable to suggest that alcohol has less effect on the young, and that it is when the age of 50 is passed that the long-term effects of alcohol are more serious. The dilated veins on the side of the nose which stand out in some who take alcohol regularly are evidence of the deleterious effect of continual small amounts of alcohol on the vascular system. But the harmful effects of alcohol probably depend most on constitution. Some have a low tolerance and some have a high tolerance. Fat persons probably have an advantage in this respect, because the concentration of alcohol in the blood is kept low by alcohol entering the fat depots. It stays in these depots until the blood concentration is sufficiently low for the depots to release the alcohol once more. In this way fat people do not depend only on their metabolism to give them protection.

However, we know that from the early fifties for the next 10 years metabolism changes in man with the diminution in the sex hormones which occurs. It is in this age that the risks of coronary disease and of hypertension increase, and it is likely that the slight toxic effects of alcohol have their greatest impact in that period.

Vitamin E and Intermittent Claudication

Q.—*Is vitamin E of value in the treatment of intermittent claudication and such conditions?*

A.—Vitamin E is considered by some to be of value in the treatment of the symptom of intermittent claudication and by others to be valueless. Throughout the last 20 years papers stating these two views have appeared regularly. The important fact is that intermittent claudication is a symptom which has a marked but limited tendency to spontaneous improvement and which varies in severity from day to day. The cause is usually an atherosclerotic thrombosis or stenosis of the superficial femoral artery. After this event intermittent claudication is first noticed and then over the next few weeks or months the distance walked before the onset of pain increases as the collateral circulation develops. Improvement ceases when the collateral circulation has fully developed, and, apart from day-to-day variations, the condition now remains stationary until a further thrombosis occurs or the flow through the occluded vessel is restored. Vitamin E, *or any other medical or surgical measure*, is bound to succeed in apparently producing improvement in many patients if given early in the course of the disease. But controlled trials of this and other preparations have shown that the improvement is not different from that in similar untreated patients. Vitamin E has the advantage that it does not produce unpleasant side-effects as some of the vasodilator drugs do, but this alone is not sufficient to justify the wide use of a most expensive drug, the value of which as a treatment for intermittent claudication is at the best unproved.

D.D.T. in Scabies

Q.—*Is D.D.T. powder of use in the treatment of scabies?*

A.—D.D.T. powder is not likely to be of value in the treatment of scabies, but D.D.T. 6% in an ointment base has been used successfully. It is applied following a bath and repeated the following day. Applicatio dicophane (*National Formulary*), though containing only 2%, would probably be effective.

Corrections.—*Public Health Laboratory Service: Diagnosis of Toxoplasmosis.* In the notice published on p. 870 of the *Journal*, March 28, the word "Sheffield" at the end of the first paragraph should be replaced by "Swansea."

The drug "brevidil M" was wrongly spelt "brevedil M" in the article "Incidence of 'Muscle Pain' After Short-acting Relaxants" (*Journal*, April 4, p. 904).

Collected Articles from the "British Medical Journal"

The following books are available through booksellers or from the Publishing Manager, B.M.A. House. Prices, which include postage, are now the same for both inland and overseas.

Emergencies in General Practice (26s. 9d.)

Refresher Course for General Practitioners, Volumes 2 and 3 (26s. 9d. each).

Clinical Pathology in General Practice (22s. 3d.).

Any Questions?, Volumes 2 and 3 (8s. 3d. each).

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